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Archives of Internal Medicine

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A STUDY OF MIXED LEUKEMIA WITH THE REPORT OF A CASE *

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MINNEAPOLIS

So-called mixed leukemia, that is, a combination of myelogenous and lymphatic leukemia occurring in one person at the same time, is such a rare condition that I have felt it worth while to report this case, as well as enter into the problem which a study of the case presents and to review the literature on previously reported cases.

Türk [1] was the first to report a case of so-called mixed leukemia. This was in 1906, before the congress of Internal Medicine. He reported four cases at this time which he considered to be mixed leukemia. He apparently was the first to appreciate, at least, to publish the fact that an activity of the lymphatic and myeloid systems could go on in an individual at the same time. In the same year, Hirschfeld [2] reported a case which he called true mixed leukemia, and in 1909, Herz [3] reported a case which he felt he could call by no other name. In 1913, Herxheimer [4] discussed the question of mixed leukemia and reported a case which he believed to be a true example. Since this time there have been various cases of so-called atypical leukemia reported, some of which may be in the classification bearing the foregoing title, but the authors have not labeled them as such.

In arriving at the diagnosis of mixed leukemia in any case, many points of discussion arise which entail opinions and theories which are vital issues among hematologists of the present day. Many prominent hematologists such as Meyer and Heineke,[5] Fabian,[6] Naegeli,[7] and

* From the Hematological Laboratory, Department of Animal Biology, University of Minnesota.

1. Türk, W.: Berichte aus den Wissenschaftlichen Vereinen, Wien. med. Wchnschr. **54**:1430, 1904; ibid., Ueber Regeneration des Blutes unter normalen und krankhaften Verhaltnissen, Zentralbl. f. allg. Path. u. path. Anat. **19**:895, 1908.

2. Hirschfeld, H.: Ueber Leukämie, Folia haematol. **3**:332, 1906; ibid., Weiteres zur Kenntniss der myeloiden Umwandlung, Berl. klin. Wchnschr. **43**: 1064, 1906.

3. Herz, A.: Zur Frage der gemischten Leukämie, Wien. klin. Wchnschr. **22**:1030, 1909.

4. Herxheimer, G.: Ueber einen combinierten Fall von lymphatischer und Myeloblastenleukämie, Zentralbl. f. allg. Path. u. path. Anat. **24**:897, 1913.

5. Meyer, E., and Heineke, A.: Ueber Blutbildung bei schweren Anämien und Leukämien, Arch. f. klin. Med. **88**:435, 1907.

6. Fabian, E.; Naegeli, O., and Schatiloff, P.: Beiträge zur Kenntniss der Leukämie, Virchows Arch. f. path. Anat. **190**:473, 1907.

7. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Edition 3, Leipzig, 1919, Ver. Wiss. Verleger.

Schatiloff [6] deny the possibility of the existence of a mixed leukemia, while other equally prominent men such as Herz,[3] Hirschfeld,[2] von Domarus,[8] Herxheimer [4] and Downey feel that they cannot explain the findings in these cases except on the basis of a true mixed leukemia. Döhrer, Pappenheim [9] and others take an intermediate position, while many do not express their opinion on the subject at all.

While studying this case, certain observations gave information and suggested opinions on the old but still acute question among hematologists; namely, the theory of the origin of blood cells. This will be discussed briefly at a later time.

Before calling a condition mixed leukemia, Browning demands proof that the myeloid and lymphatic tissue of the body must be stimulated simultaneously in the same way and in the same place, with evidence in the form of active myeloid and lymphatic metaplasia. According to this definition, I feel that the following case which I shall report must be called a mixed leukemia. I cannot see how the findings in the blood smears and histologic structures of the tissues can be explained on any other basis.

The condition occurred in a patient of Dr. F. W. Schultz, of this city, who kindly allowed me to study and report it and who gave me the following records of the case:

REPORT OF CASE

History.—R. M. W., a girl, aged 3 years, was brought to the physician for examination on Sept. 6, 1921. She was the third child of a moderate sized family; the other children and parents were living and well. She was a full term infant, of normal birth and breast fed. She had measles and whooping cough but no recent illnesses. For two weeks before examination she complained of pain in the abdomen, arms and legs. The temperature had risen in the afternoons and the patient complained of being tired and of having a poor appetite. She did not sleep well. The bowels were regular but the patient had been losing weight.

Physical Examination.—A fairly well nourished child was seen, with clear skin, firm muscular tone, normal glands, well-formed head with the fontanels closed. The throat showed some inflammation. The chest formation was good. The lungs were clear throughout. The heart was normal in area and sound. The abdomen was normal. The liver and spleen were not felt. The rectum and genitals were normal. The extremities were symmetrical, with no enlargements. The reflexes were not exaggerated.

Urine examination was negative. Blood examination showed a hemoglobin of 65 per cent.; red blood cells, 4,504,000; white blood cells, 11,400; differential polymorphonuclears, 45 per cent.; lymphocytes, 50 per cent.; mononuclears 3 per cent.; transitionals, 1 per cent.; eosinophils, 1 per cent. The Wassermann reaction was negative. The Pirquet test was negative. Another urinalysis on September 9 was also negative.

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8. von Domarus: Der gegenwärtige Stand der Leukämiefrage, Folia Haematol. **6**:337, 1908.

9. Döhrer and Pappenheim: Ein weiterer Fall von akuter Microlymphoidoztenleukämie, Folia Haematol. **16**:143, 1913.

The patient returned, September 17, at which time she weighed 31 pounds, 5 ounces (14.3 kg.) showing a loss of only 3 ounces (85 gm.) since the first visit on September 6. The coagulation time of the blood was four minutes. Urinalysis was normal. Physical examination showed a slight puffiness over the left eye. No definite tremor was palpable. The patient complained of difficulty in walking, some malaise and being always tired. She walked with some difficulty. The swelling over the left eye was becoming more pronounced. The abdomen was normal, and there was no enlargement of the spleen or lymph glands determined at this visit.

On September 17 a tonsillectomy was done. The child did not seem to make a normal recovery from this slight operation, but remained weak and continued to run a fever.

A week later there was extreme prostration, pallor, malaise and drowsiness. The spleen was enlarged to 4 inches (10 cm.) below the rib margin. There was no icterus and no general enlargement of the glands. The patient was sent to the hospital. It was at this time that acute leukemia was first suspected and the following and subsequent blood examinations confirmed the diagnosis.

On September 26, examination of feces (two specimens) showed microscopic blood present but no pus cells. A differential count was made at this time and the blood smear examined by Dr. E. L. Gardner. His report read as follows: "Five hundred cells were counted with the following results: polymorphonuclears, 6 per cent.; lymphocytes, 15 per cent.; transitionals, 1 per cent.; promyelocytes and so-called stem cells, 45.25 per cent.; myelocytes (neutrophilic), 5.5 per cent.; basophilic, 0.3 per cent.; eosinophilic, 0.3 per cent. Many nucleated red cells were noted, with quite a few degenerating leukocytes, some having the nuclei extruded. There were practically no normal cells seen. All showed signs of marked bone marrow stimulation. The red blood cells were irregular and pale with some polychromatophilia. Lymphocytes were very hard to differentiate from the small promyelocytes." A blood examination had also been made on September 24. At that time the hemoglobin was 38 per cent.; white blood cells, 97,000; red blood cells, 2,140,000. Differentials showed polymorphonuclears, 6.75 per cent.; lymphocytes, 92.75 per cent.; large mononuclears, none, transitionals, 0.5 per cent. Dr. Gardner noted that "there were some basophilic and neutrophilic myelocytes present, some poikilocytosis and polychromatophilia. There was uneven distribution of pigment in the red cells, some heavily stained, others very pale. Four nucleated red cells were seen. No basophilic stippling." (The first differential count was made by Dr. Schultz' laboratory technician. The last two smears were the only ones which were available to me for study, the others having been destroyed. The report of my study of these blood smears will be given later.)

Death occurred, Sept. 30, 1921. There were no important clinical changes during the last week of life.

The following is a copy of the necropsy, which was made by Dr. E. T. Bell, professor of pathology at the University of Minnesota. The heart showed petechial hemorrhages in subepicardial tissue. The spleen was enlarged greatly, and weighed 300 gm. There were no adhesions. The various surfaces were well defined. The capsule was smooth and clear. The cut surface was pale with reddish mottling. No definite corpuscles were visible. There was a small accessory spleen about 1 cm. in diameter in the great omentum; the cut surface had the same appearance. The liver weighed 690 gm. The capsule was smooth with yellowish mottling underneath. The cut surface was pale and mottled with regular yellowish spots about from 1 to 2 mm. in diameter. The gallbladder was normal. The abdomen and intestines showed numerous petechial hemorrhages on serosa of the intestinal coils. There was a partial intussusception in part of the ascending colon in which the ileum was invaginated into the cecum and ascending colon. At the head of the intussusception was a large polypoid mass. The gastric juice was of a reddish-brown color suggesting the presence of blood. There were no changes in the small intestines. The intussusception

was evidently agonal. On opening this portion of the intestines, a polypoid mass was found at the head of the invaginated portion and attached to the wall of the cecum near ileocecal valve. The mass measured 4 by 3.5 by 1.5 cm. There was a central ulcerated area 3 cm. wide. The mesenteric and preaortic lymph nodes were enlarged. The largest was 5 by 3 by 2.5 cm. The next largest was 2 by 2 by 2 cm. A number of small lymph nodes showed no change. In the base of the mesentery, the enlarged nodes were crowded closely together, forming a large tumor mass which was evidently the mass palpated through the abdominal wall. There were no other enlarged lymph nodes. The pancreas and adrenals were normal. The kidneys weighed 55 gm. each, and were pale and cloudy. There was a small tumor mass in each, palpable and visible after capsule was removed. The bladder was normal. The ovaries were greatly enlarged. The thymus was not enlarged. The brain was normal, with numerous small infiltrated areas in the dura mater which eroded the underlying bone.

Microscopic Examination.—The large lymph nodes of the mesentery showed leukemic infiltration, necrosis and hemorrhage. The small mesenteric nodes showed leukemic infiltration. The polypoid mass in the cecum showed leukemic infiltration of the mucosa. The liver showed portal leukemic infiltration. The spleen showed leukemia infiltration of a large portion of the pulp; the corpuscles were indistinct. The kidney showed small nodules composed of lymphocytes. There were albumin casts in the lumina of the tubules. The pancreas showed small areas of lymphocytes. The diagnosis was acute myeloid leukemia.

MICROSCOPIC STUDIES

The blood smears were sent to Dr. Hal Downey who, on examining them, immediately perceived that there was something unusual about the case. He saw in the blood smears all stages of developing myeloid and lymphoid cells, and it was at his suggestion and under his supervision that I have made an intensive study of this case.

Material and Staining.—Sections of the following tissues were available for examination: Polypoid mass in cecum, an enlarged mesenteric lymph node, spleen, liver, lung and kidney. They were all fixed in formaldehyd and stained according to the method of Dominici.

Only two blood smears were available for examination, as mentioned before. Ordinary Wright's stain was used in preparing them.

Intestinal Polypoid Mass Found in the Cecum.—Sections through this mass showed it to be due to an infiltration of leukemic cells into the mucosa. Most of the cells present were lymphocytes, although there were a few myelocytes and adult eosinophils seen. Necrosis was quite marked, especially in the small cells.

Lymph Nodes.—Sections through various portions differed somewhat, but I shall describe only two of the more typical areas.

1. In this area there were no definite follicles, but there was a general increase in the lymphatic tissue, which was spread out diffusely over the entire section. There were some areas suggesting follicles which had atrophied, with marked evidence of necrosis. The reticular tissue on the whole was filled with lymphocytes in various stages of development. No myelocytes were seen in the interfollicular or medul-

lary tissue, but some of the large blood vessels contained a few. In some areas the lymphocytes were more condensed and here mitosis was common.

2. The other most typical area showed a relative increase of the interfollicular tissue or pulp over that found in the foregoing area described. Atrophy of the follicles was more marked. The dying follicles showed marked necrosis of cells with no evidence of mitosis. Mitotic figures in the lymphocytes were not so much in evidence in this section. The lymphatic tissue was, as a whole, a little more dense and concentrated. The interfollicular tissue showed many myelocytes mostly of the eosinophilic type. They were scattered diffusely in the reticular tissue of the medulla with no special relation to the blood vessels. In general, there could be no definite distinction made between the cortex and medulla or the cells in these areas. The predominating cell was the medium sized lymphocyte, although some small and large lymphocytes were present. Many of the myelocytes show small dark-stained nuclei, rich in chromatin, which were indistinguishable from the nuclei of many of the adjacent lymphocytes. Most of the lymphocytes present were of the typical adult type, but there were some young lymphocytes scattered here and there among the former (Fig. 1).

Lung.—The various sections were about the same. There was no evidence of lymphoid follicle formation. The connective tissue of the alveolar walls contained many large typical eosinophilic myelocytes and some with smaller fine red granules, undoubtedly neutrophilic myelocytes. There were some other cells present in the reticular tissue which had a dark, purple staining, slightly irregular nucleus which was about the same size as those found in the myelocytes, but the chromatin was more dense and in irregular masses. The protoplasm took a basic stain and formed in a narrow ring about the nucleus. They were undoubtedly early or young lymphocytes. Also many cells were seen with dark, pyknotic, round nuclei, showing more cytoplasm taking the basic stain. They were undoubtedly adult lymphocytes. Many of these cells could be seen undergoing mitosis. Adult eosinophils were also seen in the reticular tissue. Some of the alveoli were filled with blood and showed cells similar to those found in the blood smears. Large phagocytic cells were also seen.

In general, we found here a myeloid and lymphatic reaction or activity in the reticular tissue, with the former predominating slightly. Local development of myelocytes and lymphocytes was in evidence.

Kidney.—A typical section showed areas of marked leukemic cell infiltration, with atrophy of tubules and glomeruli, and many necrotic cells present. The infiltration was diffuse with no evidence of follicular arrangement. The great majority of the leukemic cells were lympho-

cytes, small, large and medium in size, with the latter predominating. There were some immature ones among them. An occasional lymphocyte showed mitosis.

There were cells which were a little larger than the adult lymphocyte, which had only a small ring of cytoplasm about a large nucleus which was very poor in chromatin, and had a very fine nuclear membrane. The nucleus was pale in appearance with only here and there a fine dot or strand of chromatin visible. I interpret this type as being the most immature cell present; it corresponds to the description of the "stem" cell as seen in the tissue. There were other cells, mixed in with

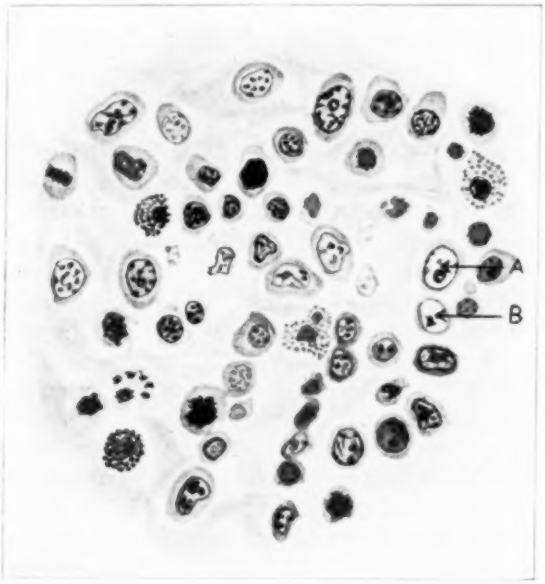

Fig. 1.—A typical area in one of the enlarged mesenteric lymph nodes. Stem cell (*b*), immature lymphocyte (*a*), eosinophilic myelocytes, cells undergoing mitosis and degenerating cells are mixed together. Below cells *a* and *b* are three maturing lymphocytes, more mature than cell *a*.

these, showing just a little heavier nuclear membrane and just a little more chromatin within the nucleus, which I interpret as being somewhat more matured. Representative cells of succeeding stages in the differentiation of these lymphocytes to a typical adult lymphocyte were seen.

Scattered about between these developing lymphocytes were many neutrophilic and eosinophilic myelocytes. They were found in the tissues between the tubules, away from the blood vessels, and an occasional adult eosinophil or neutrophil was also seen. In these same areas

there were many cells with small, dark staining nuclei resembling the small lymphocyte in the tissue but having eosinophilic granules in the cytoplasm. Some of the granules were very young as was evidenced by the basophilic staining reaction.

There were also a few red blood cells scattered about in the tissues but no areas of hemorrhage. In the areas undergoing necrosis the leukemic cells as well as the kidney structures were affected (Figs. 2 and 3).

Fig. 2.—A low power view of the kidney, showing the nature of the leukemic cell infiltration. Note the atrophy of kidney structure.

Pancreas.—A typical section showed several small areas where pancreatic cells were undergoing atrophy and necrosis with replacement by connective tissue. There was infiltration of the leukemic cells in the connective tissue between the lobules, but no evidence of follicular arrangement. These areas showed a mixture of interesting cells. There were many eosinophilic myelocytes and neutrophilic myelocytes as well as mature cells. These eosinophilic myelocytes were of all sizes,

from that of typical eosinophil to that of the smallest lymphocyte. Many of them had a single small nucleus darkly stained and very rich in chromatin, very similar to those seen in lymphocytes in that same area. Occasionally two such cells, that is, an eosinophilic myelocyte and a lymphocyte could be seen side by side with the nuclei apparently identical. Some of the myelocytes as well as the lymphocytes had pyknotic nuclei and seemed to be degenerating. In these same areas, mixed in

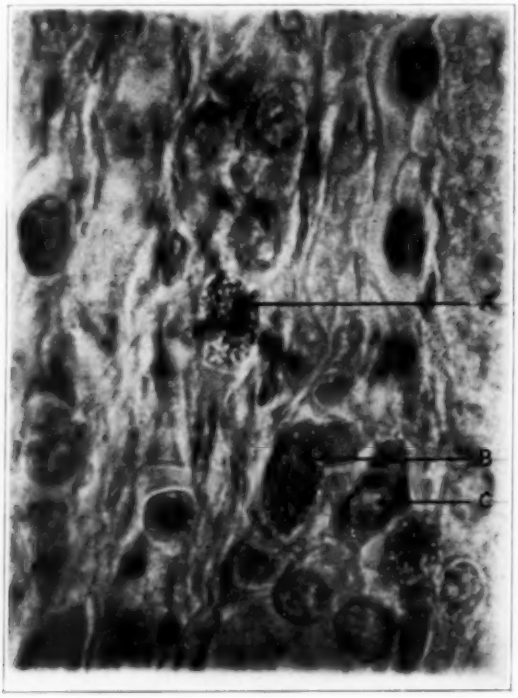

Fig. 3.—This is a higher magnification of a small area in Figure 2 marked thus □. The types of cells present and some of their characteristic features can be seen. Cells *a* and *b* are eosinophilic myelocytes. Cell *c* is an immature lymphocyte.

with the myelocytes, were many lymphocytes in various stages of development. The so-called "stem" cell as it appears in the tissue was also seen here and had the same characteristics as given in the description of these same cells found in the kidney. Many immature lymphocytes were seen. These young or early lymphocytes were very poor in chromatin with a thin nuclear membrane, and here, even more so than

in the kidneys, showed definite nucleoli, some only one, while others had even two or three. Here, as elsewhere, the medium size lymphocyte was the predominating cell.

In a few places the leukemic cells had infiltrated between the acini near the edge of the lobule, but on the whole the leukemic infiltration was limited to the interacinar connective tissue spaces. These were apparently widened in some places and occasionally showed small areas of hemorrhage. The blood vessels of the pancreas were filled with

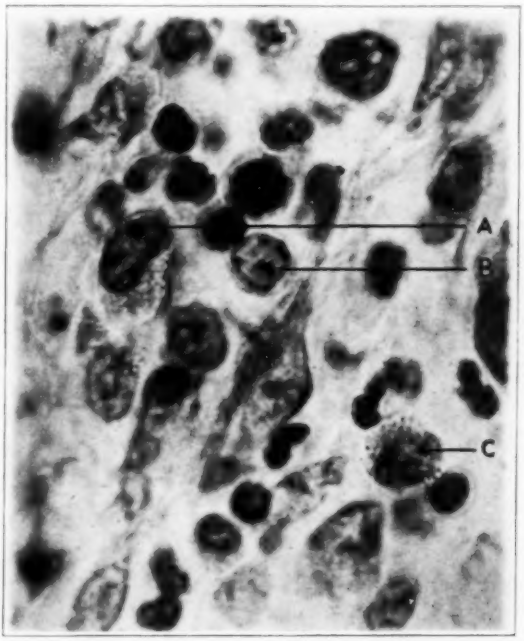

Fig. 4.—A typical area showing the character and distribution of the leukemic cells in the interacinar connective tissue in the pancreas. Cells *a* and *c* are large eosinophilic myelocytes. Cell *b* is an immature lymphocyte. Stem cells are also present in this general area, but their characteristics are not brought out by photomicrograph. Dividing cells with mitotic figures and degenerating cells with pyknotic nuclei can be seen.

leukemic cells of the same type as those found in the blood smears and interfollicular tissue.

In general, myeloid cells and lymphocytes were diffusely arranged and mixed together in the interacinar connective tissue (Fig. 4).

Spleen.—Here as in the lymph node, sections through different parts appeared somewhat different and two typical ones will be described.

1. The first typical section was one showing a general increase in the lymphoid tissue with a scarcity of pulp or interfollicular tissue. No definite follicles were seen but rather was there a large overgrowth of the lymphoid tissue, with large diffuse areas of lymphocytes which in a normal spleen would be follicles. These areas had arms, or branches, extending out into the pulp connecting with arms of other similar areas forming a kind of a network. The diffuse lymphatic follicular

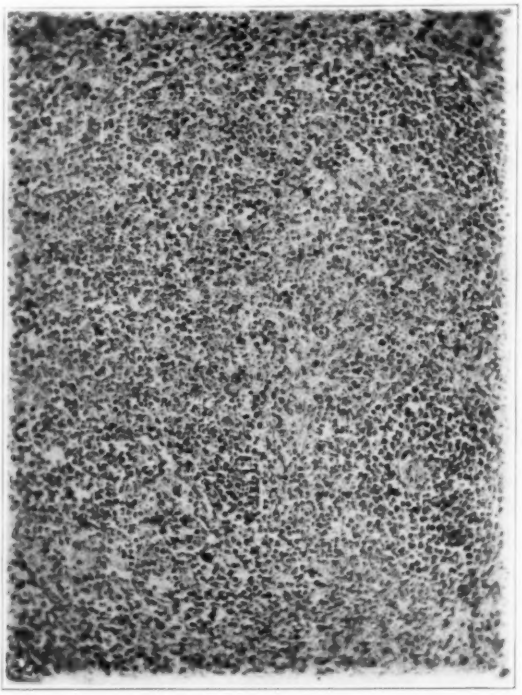

Fig. 5.—A low power view of a typical area in the spleen, showing the general distribution of the cells. Note the absence of definite follicles and the general increase in the lymphoid cells. In the lower right hand corner can be seen a blood vessel with a condensation of lymphocytes about it.

tissue was in much larger amount than the pulp and the total amount of lymphatic tissue was greater than found in a normal spleen. In some areas, the line of demarcation between the pulp and these diffuse lymphocytic areas was more marked and easily definable. There were several hemorrhagic areas of various sizes, some being quite large. There were several areas of accumulation of lymphocytic cells along the course of the blood vessels, and when seen in cross-sections they appeared as fol-

licles, but on studying them more closely, it was easily seen that they were not typical. The predominating cell here, as elsewhere, was the medium size lymphocyte although there were many small and large types also.

However, in the areas of concentration of lymphocytes, I found eosinophilic and neutrophilic myelocytes as well as adult eosinophils. They were mixed diffusely with the proliferating lymphocytes. Myelo-

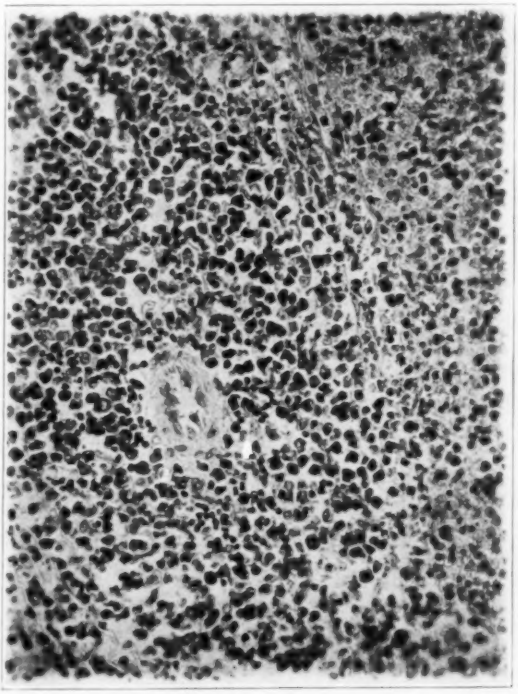

Fig. 6.—Is a higher magnification of Figure 5. It is interesting to note that even in this area of condensation of lymphocytes, many myelocytes were found, although they cannot be distinguished at the magnification of this photomicrograph.

cytes were present, however, in larger numbers in the interfollicular tissue or pulp.

2. The other typical section was somewhat different. It showed an enormous amount of lymphoid tissue with very little pulp. Necrosis was more marked here. There were large hemorrhagic areas. Fibrosis was more extensive. Red blood cells were scattered diffusely throughout the lymphatic tissue. The predominating cell was the medium size

lymphocyte. Mitosis was occasionally seen. Some myelocytes and adult cells were seen but not so many as in the previous section. Some of these were also undergoing degeneration as indicated by their pyknotic nuclei.

In general, the lymphatic tissue predominated throughout the spleen although in some areas the pulp was much more in evidence than in others. There were several small areas seen where the pulp predominated. There was diffuse hypertrophy of lymphoid tissue throughout.

Fig. 7.—A low-power view of an area of the spleen where the pulp tissue slightly predominates, showing the diffuse distribution of the cells. Many myelocytes can be seen under high power oil immersion magnification but the medium-sized lymphocyte is the predominating cell. The border of a large hemorrhagic area in the upper portion of the field can be seen.

The malpighian bodies were apparently replaced by a concentration of lymphocytes along the course of the arteries. In cross-sections these appeared like malpighian bodies of the normal spleen, but they had no germinal center and were not so dense as normal follicles and contained relatively few small lymphocytes, most of them being medium, with a

few large ones. It was in these areas that the myelocytes were seen as well as in the pulp or interfollicular tissue. On the whole, there was a total increase in the lymphatic tissue over that of the normal spleen. Myeloid metaplasia was present in these areas of "lymphocytic concentration," but was much more extensive in the pulp. Lymphatic hyperplasia predominated (Figs. 5, 6 and 7).

Fig. 8.—A low-power view of the liver, showing the interlobular leukemic cell infiltration and atrophy of some of the liver cells.

Liver.—The interlobular spaces were filled with leukemic cells and the latter filled many of the adjacent sinusoids. Otherwise, the sinusoids were free from cells. These masses of cells were composed mainly of lymphocytes in various stages of development. Some of them showed mitotic figures. Only an occasional myelocyte was found mixed in with the lymphocytes. Most of the lymphocytes were of medium size with relatively few large and small types. Degenerating forms with dense

pyknotic nuclei were seen. Mitosis was common. Necrosis of some of the cells was also found in areas but not to the extent found in other organs. Again we found cells here that had large nuclei with very little chromatin, a thin nuclear membrane and a few nucleoli. They had only a narrow rim of cytoplasm and were almost identical with the so-called "stem" cell as seen in the tissue (described before and found in other organs). Various stages of developing lymphocytes were found here. A few nucleated reds were seen with many adult red blood cells. No definite areas of hemorrhage were seen, however.

In general, there were extensive areas of leukemic infiltration limited to the interlobular spaces and a few adjacent sinusoids. The interlobular spaces were increased in size, which increase was probably due to pressure from the masses of leukemic cells. In some places the leukemic cells almost surrounded the lobules of the liver, making them very prominent. There was no local development of the cells in the sinusoids and they were not enlarged. There was no definite follicular arrangement of the leukemic cells (Fig. 8).

No sections of bone marrow were obtainable.

Blood Smears.—There were only two smears available to me for examination. One was taken on September 24, at which time the leukocyte count was 97,000. The other smear was taken on September 26, four days before death, which occurred on September 30. The leukocyte count was not taken at the time the last smear was made. It is interesting to note that the differential counts on the two occasions were quite different, the first one showing a predominance of the myeloid elements while the second one showed a relative increase in the young lymphocytes. I will first describe the more important cells seen before giving the differential counts of the different cells.

Blood Smear, Sept. 24, 1921.—On looking over this smear I was immediately impressed by the predominance of a cell which I wish to describe in detail. The size varied from that of a small lymphocyte to that of an ordinary large mononuclear cell. The nucleus was large and spherical and practically filled the cell leaving only a narrow ring of deep bluish cytoplasm, the latter occasionally containing vacuoles. Twenty per cent. of these cells showed a peculiar type of azure granulation described by Pappenheim [10] (Fig. 9 *c*).

The nucleus as described filled most of the cell, but the striking feature was the diffuse distribution of the chromatin. It was in the

10. Pappenheim: Atlas. Die Zellen der leukämischen Myelose, Jena, Gustav Fischer, 1914. 1. "Stem" cells: Plate XIV, Figs. 1 and 27. 2. Myeloid azure granulation: Plate XVIII, Figs. 1 and 5. 3. Leukoblasts: Plate XIV, Column B. 4. Promyelocytes: Plate XIV, Column C, Rows a and b. 5. Micromyeloblasts (of Pappenheim): Plate XVI, Figs. 12 and 13. 6. Myelocytes: Plate XIV, Figs. 11, 24, 48 and 73.

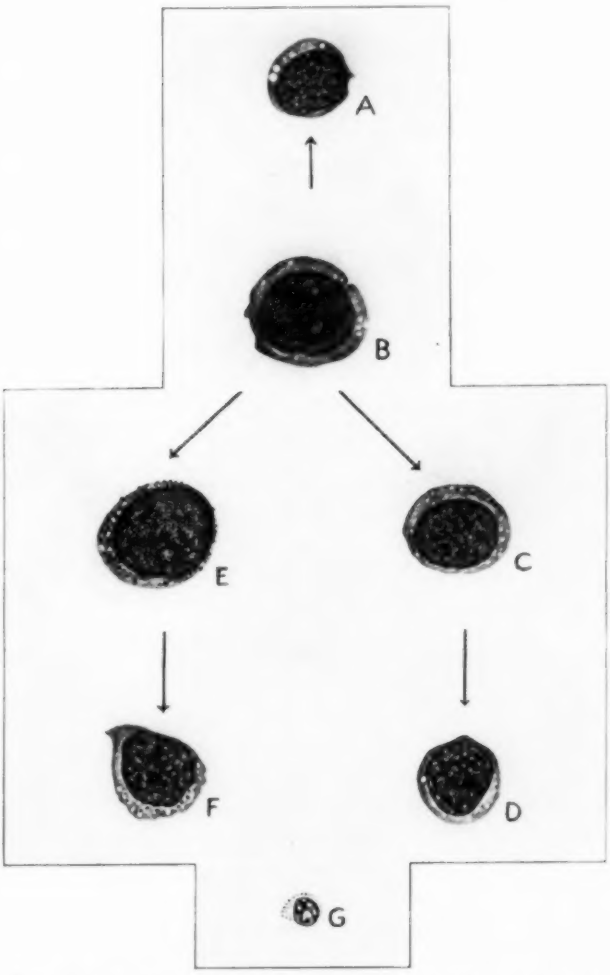

Fig. 9.—Drawing of cells from the blood smears. (*a*) Immature lymphocyte, smaller type, probably developing from a micromyeloblast (a cell similar to the one *b*, only smaller). (*b*) Lymphoidocyte or "stem" cell. (*c*) Immature lymphocyte, representing an early stage of development from type of cell as shown in *b*. (*d*) Immature lymphocyte, representing a later stage of development than *c*. (*e*) Leukoblast, showing azure granulation. It represents the first stage in the development of myeloid cells from the stem cell. (*f*) Promyelocyte, a cell representing the second, or later, stage in the development of myeloid cells. (*g*) A small eosinophilic myelocyte seen in the intra-acinar connective tissue of the pancreas. It is the same size as neighboring lymphocytes, with a nucleus identical in appearance with that found in these lymphocytes.

form of an extremely delicate network giving the nucleus the appearance of a fine mesh sieve. Many of the cells contained nucleoli, but not all, and when present they varied in number. Thirty-four per cent. of the cells counted were of this type. This cell corresponded to the so-called lymphoidocyte of Pappenheim [10] as shown in his atlas, and in Figure 9 *b* accompanying this paper.

The next most common cell (15 per cent.) was one about the size of a small lymphocyte, having a very narrow ring of basophilic cytoplasm, in fact, in many instances the cytoplasm could not be seen at all, the nucleus apparently entirely filling the cell. The nucleus itself was rich in chromatin but the latter was evenly distributed throughout the nucleus with no areas of condensation. Occasionally a nucleolus was present. This cell corresponds in every detail with the micromyeloblast of Pappenheim.[10]

There were a number of cells which greatly resembled the previously described, so-called "stem" cell, but the chromatin was not so finely distributed and showed a tendency to form in strands. There was also a greater proportion of cytoplasm in the cell, the latter not containing, as a rule, so many of the coarse azure granules. Nucleoli were seen but they were not so many or so distinct as in the stem cells. This type of cell I interpret as a leukoblast. Five per cent. of the cells present were of this type [10] (Fig. 9 *c*).

Other somewhat similar cells with more abundant, but not so basophilic cytoplasm showed beginning acidophilia in some places. The nucleus was not so large in proportion to the amount of cytoplasm and was usually not spherical. The characteristic feature of this cell was also the "network" distribution of the chromatin in the nucleus. It was also formed in strands, but these were much coarser than in the case of the leukoblasts. The network might be compared to a very coarse, heavy mesh sieve. Nucleoli were rare, although occasionally seen, as was the case with the coarse, azure granules. The distinctive point of difference between this cell and the leukoblasts was the more marked coarseness of the strands of chromatin and the beginning acidophilic staining of the cytoplasm. This cell corresponded to the promyelocyte and was present in the same percentage as the leukoblasts [10] (5 per cent.) (Fig. 9 *f*).

Myelocytes of all types, neutrophilic, eosinophilic and basophilic were present. Some cells, however, showed an apparent unequal maturing of the cytoplasm and nucleus; for example, the nucleus would be in the promyelocyte stage and the cytoplasm contain typical myelocytic granules, and vice versa. Fully differentiated typical neutrophils, eosinophils and basophils were also present. Some of the neutrophils were apparently degenerated as indicated by pyknotic nuclei. The adult cells

were of varying sizes. It was very easy to pick out a series of myeloid cells in all stages of differentiation from the stem cell to the full-grown adult neutrophil or eosinophil.

The lymphocytic series was also well represented in this smear with examples of the various stages of development. The earliest type found was one which resembled a stem cell, only the cytoplasm was larger in amount and of a lighter blue color, and the azure granules were not so abundant and were finer, nonangular and of a pinkish-red rather than the deep purple of the stem cell. The distribution of the chromatin was the most characteristic point of distinction. Here the chromatin was more abundant, took a deeper stain and was spread over the nucleus in a manner which one might describe as "blotchy," there being areas of condensation of chromatin. As a whole, the distribution of the chromatin in the nucleus had a spotted appearance, in counter distinction to the fine network in the stem cell or the coarser sieve-like appearance in the leukoblasts (Fig. 9 *c*).

From this early type could be traced a series of developing lymphocytes to the mature form as seen in normal blood, but the various stages could not be so easily distinguished or defined as in the myeloid series. Progressive differentiation was characterized by an increase in the amount of chromatin, in its blotchy distribution and by an increase in the relative amount of cytoplasm which took a lighter bluish stain. There were many examples of the large typical adult lymphocyte which needs no description (Figs. 9 *a, c* and *d*).

In addition to the foregoing described types of cells there were some which could not be classified definitely because of their atypical appearance, and so were not included in my differential count. If they had been, I would have put them in an indeterminate group. The main difficulty in classifying them was owing to the fact that they had some characteristics of the myeloid type of cells as well as of the lymphocytes. For example, the cell would have a lobulated nucleus like that of a late myelocyte or early adult neutrophil but the cytoplasm of a lymphocyte and vice versa. There were some cells seen which had the characteristics of a myelocyte but the granulation was atypical. Of course, there were degenerating cells of all types especially the neutrophils, which showed very pyknotic nuclei.

The red cell series was like that in any typical case of acute leukemia, with nucleated cells in various stages of development and many nonnucleated cells showing marked polychromatophilia, anisocytosis and poikilocytosis. Most of the cells showed pale centers and were poor in hemoglobin. Mitosis was occasionally seen in the blood.

The later blood smear which was at my disposal for examination showed the same types of cells as before described, only in different proportions. Here it is interesting to note that there was a relative

decrease in the myeloid elements of the blood with an increase in the immature lymphocytes. In this blood smear the series of developing lymphocytes could be more easily made out than in the previous one, beginning with the stem cell and ending with the adult lymphocyte. The differential counts of the two blood smears are given below.

TABLE 1.—*First Smear, Taken Sept. 24, 1921. Differential Count (300 Cells)*

	Per Cent.
Large lymphocytes	2.00
Small lymphocytes	13.3
Large mononuclears	None
Transitionals	1.00
Neutrophils	3.7
Neutrophilic myelocytes	10.00
Eosinophils	1.3
Eosinophilic myelocytes	1.7
Basophils	0.7
Basophilic myelocytes	0.3
Micromyeloblasts	15.00
So-called "stem cells"	34.00
Promyelocytes	5.00
Leukoblasts	5.00
Immature lymphocytes	7.00

TABLE 2.—*Second Smear, Taken Sept. 26, 1921, Differential Count (300 cells)*

	Per Cent.
Large lymphocytes	2.5
Small lymphocytes	22.00
Large mononuclears	0.5
Transitionals	0.5
Neutrophils	2.5
Neutrophilic myelocytes	3.00
Micromyeloblasts	17.00
So-celled "stem cells"	7.5
Promyelocytes	7.5
Leukoblasts	2.00
Immature lymphocytes	35.00

No eosinophils or basophils or their myelocytes.

Before reviewing the previously reported cases of so-called mixed leukemia, I will review briefly the important points in my own case which have led me to believe that I am dealing with a case of true mixed leukemia.

First, let me condense the important findings in the blood smears. These are not only interesting but very striking. Their importance cannot be exaggerated, as it was by means of examination of the blood smears that the true condition was first appreciated. On the first examination of the blood smears by Dr. Gardner, the condition appeared to be one of acute myeloid leukemia, but even he noted that the lymphocytes were very hard to differentiate from cells in the myeloblast stage.

Without careful study and working out a typical series, beginning with the stem cell and ending with either the adult lymphocyte or granular leukocyte, it would be difficult to determine the true condition present. The most important discovery in the examination of the smear was the presence of both types of immature cells; that is, the lymphoid and myeloid forms. It was this feature that attracted the attention of Dr. Downey when he examined the smear, and he was the first one to appreciate and interpret their importance and to realize that here was a probable case of true mixed leukemia. More careful study of the blood smears only emphasized the facts already stated—that on the one hand there was a complete series of cells representing the various stages of myeloid development from the original stem cell to the full-grown granular leukocyte; and on the other hand just as definite a series could be found showing developing lymphocytes beginning with the same stem cell and ending with the typical completely differentiated lymphocyte. A few atypical cells were present, but their importance will be discussed a little later on.

The other important point to note about the blood was that in the earliest smear the myeloid element of the blood predominated, while later on as death approached, the lymphoid and myeloid elements played a more equal part with the former slightly predominating.

The more important gross pathologic findings were a greatly enlarged spleen, petechial hemorrhages scattered throughout the body, marked enlargement of many of the mesenteric and pre-aortic lymph nodes, a leukemic polypoid mass in the cecum, and kidneys showing evidence of leukemic infiltration. From the gross findings, one might easily consider the case as that of a simple acute myeloid leukemia.

SUMMARY OF MICROSCOPIC FINDINGS

The most important feature of the involved lymph nodes was a disappearance of the typical follicle, probably due to a general increase in the lymphatic tissue which was spread out over the entire section. Lymphoid hyperplasia was the predominating feature, but myelocytes were found in the interfollicular tissue, in rather large numbers in some areas.

The reticular tissue of the alveolar walls in the lungs showed typical myelocytes and immature lymphocytes mixed together in the various stages of development. This local development of myelocytes and lymphocytes in the same areas almost side by side strongly points to a condition of mixed leukemia.

The same condition was found in the kidneys in the areas of leukemic cell infiltration, but was even more marked here than was the case in the lung tissue.

The findings in the pancreas emphasize the same thing, and here again we found myelocytes and immature lymphocytes side by side in the interacinar connective tissue, and in addition, cells of the myeloblastic type. The similarity in the nucleus of some of the eosinophilic myelocytes with those of the adjacent lymphocytes suggests that they may originate from the latter.

Again in the spleen we found evidence of myeloid and lymphoid metaplasia going on not only side by side but actually mixed together. There was an increase in the lymphatic tissue in general, with a replacement of the normal follicles by huge masses of lymphoid tissue. Concentration of lymphoid tissue about some of the large blood vessels suggested follicles when seen in cross section. The pulp tissue predominated in certain areas and here the myeloid metaplasia was more in evidence, but myelocytes were also frequently found mixed in with the masses of lymphoid cells. Nowhere was there a distinct line of demarcation between the lymphoid and myeloid activity.

The findings in the liver resembled very closely those of ordinary acute lymphatic leukemia, with the interlobular spaces filled with leukemic cells and the sinusoids free in general, with only a few myelocytes.

The lymphoid picture predominated in the leukemic infiltration in the polypoid mass found in the intestines. Evidence of degeneration found in the various organs was no different than that met with in ordinary cases of acute myeloid or lymphatic leukemia.

Viewing the situation as a whole we found some of these organs showing a predominance of myeloid activity, while the lymphoid elements were more in evidence in others; but both were definitely present in all with the possible exception of the liver and the polypoid mass in the intestines. There was evidence of irritation of both systems in all the organs examined. (It is regretted that the bone marrow was not obtainable for study in this case.) But most important to note was the mixing together or diffusion of the immature cells of both systems, with no definite line of demarcation between the two. It was because of this persistent striking feature that I feel justified in calling this case one of true mixed cell leukemia.

LITERATURE

Before going into detail in the discussion of the evidence present in this case in favor of a true mixed cell leukemia, I should like to review briefly previously reported cases bearing this name. Although there were several cases of atypical or mixed cell leukemia recorded in the literature before Türk [1] reported his case in 1906, he was the first to publish what he believed to be a case of true mixed leukemia. This case began with a typical picture of a myeloid leukemia both from a clinical standpoint and a microscopic study of the blood. The spleen was

greatly enlarged, the lymph glands normal in size. The leukocyte count went up as high as 373,000 with 90 per cent. myelocytes. Under intense arsenic therapy the leukocyte count dropped until it reached a stage of almost a leucopenia. At one time there were only 3,500 cells counted. About eight months after the disease started the picture began to change. Clinically, the lymph glands began to enlarge and the blood picture showed an increasing number of large atypical nongranular cells, with a single nucleus which often showed pale nucleoli (immature lymphocytes). The percentage of myelocytes in the blood decreased. Türk speaks of these cells as being of the character of lymphoid cells found in acute lymphomatosis. Shortly before death, these cells formed 20 per cent. of those present while there were only 3 per cent. myelocytes. He believes that the lymph glands were in a stage of at least temporary acute leukemia. He closes his report by saying that here he has a case of chronic myeloid leukemia where eventually an acute lymphoid leukemia entered. He suggests a possible cause for the entrance of the lymphoid leukemic process, saying that it may be due to an exhaustion of the myeloid elements.

Although it appears that Türk had a mixed form of leukemia, he did not have histologic studies of the organs to verify it. This is the main argument of Naegeli, Pappenheim,[11] Meyer, Heineke, von Domarus and others who disagree with him. Naegeli [12] states that histologic studies of such a case might show the apparent lymphoid tissue to be myeloid tissue. Fleischman [13] believes his case was myeloid leukemia with an increase in proportion of lymphocytes in the blood because of a deficiency in the bone marrow. Herz [3] believes that the existing stimulation producing activity of one type of tissue could cause an activity of the other type as well. Türk reported several other cases similar to the one described above.

Hirschfeld [2] was the only one who thought that Türk had a case of the true mixed form of leukemia, and gave for further proof of the existence of this type a report of a case seen in 1909. The leukocyte count was 34,000 with the percentage of lymphocytes varying from 55 to 89 per cent. He found lymphadenoid metaplasia of the bone marrow along with myeloid metaplasia of the lymph glands and spleen pulp with a blood picture of lymphocytic leukemia. Many nucleated reds were found in the lymph glands. He felt that the lymphatic leukemia in this case was primary and probably the source of the myelogenous activity.

11. Pappenheim, A.: Bemerkungen zur Frage der akuten Myeloblastenleukämie und Leukosarcoma, Wien. klin. Wchnschr. **25**:163, 1912.
12. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Ed. 2, Leipzig, Veit and Company, 1912.
13. Fleischman, P.: Der zweite Fall von Monocyten Leukämie, Folia Haematol. **20**:17, 1915.

The bone marrow changes probably occurred first, as shown by the early marked anemia, then, changes occurred in the spleen and liver, and last in the lymph glands. He believes his case to be an example of a true form of mixed myelogenous and lymphatic leukemia. His findings of myeloid metaplasia in the splenic pulp and lymph glands was similar to what I found in my own case. In conjunction with the lymphadenoid metaplasia, which he found in the bone marrow, and the blood picture, I believe that he is justified in calling his case one of true mixed leukemia. Hirschfeld also showed that there was a continuous series of transitional forms leading from the typical acute lymphocytic leukemia to the acute mixed cell type of leukemia. (He modified this observation later.) Meyer, Heineke, Fabian, Naegeli, Schatiloff and Pappenheim disagree with Hirschfeld and claim that the myeloid tissue in his case was squeezed out of the bone marrow through hyperlymphadenoid activity, and was thus transplanted into other places where it proliferated vicariously in the extramedullary organs.

In 1909, Herz [3] reported a case. The clinical symptoms were those of acute leukemia with enlargement of the lymph glands on the right side of the neck and no enlargement of the spleen. There were 51,000 leukocytes and 45 per cent. nongranular cells with large single nuclei. In later counts the neutrophilic myelocytes increased from 5 to 16 per cent. and the large nongranular cells increased to 54 per cent. The histologic findings were as follows: the bone marrow showed an activity of the myeloid tissues with neutrophilic granular myelocytes and nongranular myeloblasts. In the middle of the myeloid tissue he found groups of cells that had all the characteristics of the small lymphocyte. They were the same type of lymphocyte as found in the follicles of the spleen. However, the border line between these "herds" or groups of lymphocytic cells and the myelocytes was rather sharp. The spleen showed typical myeloid changes in the pulp with suppression of the follicles, but the latter could still be seen although they were small. The lymph glands showed a picture often seen in chronic lymphatic leukemia with the structure gone, follicles and interfollicular tissue indistinguishable. Most of the cells were proliferating lymphocytes. No germ center cells were seen. In the center of these condensations of lymphocytes, he found large cells with a single nucleus which he interpreted as neutrophilic myelocytes. In one pulmonary lymph gland he found a marked activity of the lymphoid tissue with a moderate activity of the myeloid element. The liver in this case showed small groups of so-called myeloblasts in the interlobular tissue. Herz calls his case one of mixed leukemia because of the simultaneous appearance of both types of tissues in the bone marrow, with a definite diffuse myeloid hyperplasia and lymphatic activity, and further because of the myeloid metaplasia in the

spleen and lymphoid metaplasia in the lymph glands, the latter also showing myeloid metaplasia.

Von Domarus [5] agrees with Herz in his diagnosis, but Naegeli [7] again disagrees, saying that the appearance of the myeloid cells was agonal or a dispersion of marrow cells due to sepsis, as an endocarditis was found at necropsy. Herz admits that sepsis can explain the acute lymphatic leukemia followed by a myeloid leukemia but he does not believe it can explain a myeloid metaplasia in the bone marrow, spleen and lymph glands as was found in his case. Herz concludes by stating the fact that, along with many lymphocytes an important number of the elements of myeloid tissue was present in the blood, and in addition, activity of both types present in the hematopoietic organs proves that there must be a disease of both types of tissue; that is, a mixed leukemia. It was these facts that made Herz call his case mixed leukemia.

The next case of mixed leukemia was that reported by Herxheimer.[4] The white count was 72,000. The differential showed most of the cells to be small lymphocytes but with 25 per cent. myeloblasts. He also found many small cells with a single nucleus which stained very dark and had little, if any, structure. They had a very narrow cytoplasm. He interpreted these as being micromyeloblasts or very young, small lymphocytes. He interpreted the large cells, with a single nucleus having a distinct clear, fine structure and many nucleoli, as being myeloblasts. Most of the cells in the bone marrow were lymphocytes but there were some myelocytes and developing red blood cells. The extramedullary organs showed evidence of myeloid and lymphatic activity. Necropsy showed no evidence of sepsis, but a large leukemic mass in the mediastinum in which the thymus was obliterated. He concludes that his case could be interpreted as one of the small cell leukemias if it were not for the presence of myelocytes in the various organs, even including the mediastinal tumor. He believes that first there was a lymphatic leukemia and later the entrance of a myeloblastic leukemia with a tendency toward tumor-like activity, especially in the mediastinum, and that his case, like those of Hirschfeld and Herz, is an example of true lymphatic and myeloid leukemia.

Naegeli [7] and his followers, not believing it is possible to have a mixed leukemia, explain Herxheimer's case on the basis of a compensatory activity of the "stem" cells, or immature leukocytes following their expulsion from the bone marrow, as is observed in lymphatic leukemia and toxic anemia. They again offer the explanation that the myeloid cells are the result of a vicarious activity of displaced bone marrow myeloid tissue in the extramedullary organs. Herxheimer does not believe that his case can be explained by a simple passing out of cells into the blood, as was spoken of in Herz's case, as there was no septic cause for this in his case. He does not see where the proof has been

given for Naegeli's idea of the vicarious activity of displaced bone marrow myeloid tissue, and that this idea is no better than his own, namely, that this case is one of a true mixed leukemia. He does not believe that we can definitely say whether it is a vicarious activity or not until we know the cause and origin of leukemia. Because of the distinct separation of the local development of the lymphocytes and granular leukocytes, even though they are side by side, the farthest he wants to go is to call his case one of combined leukemia, and he leaves the question open as to the cause of the appearance of the latter form of leukemia, in his case the myeloblastic leukemia; that is, whether it is a compensatory entrance or not.

De Castello [14] reports a case of mixed leukemia, where a leukopenia developed under the use of roentgen ray and lymphocytes entered. Naegeli and Pappenheim [15] explain this by assuming that there was a de-differentiation of the myeloid cells.

In 1905, Browning [16] reported a case which he called mixed cell leukemia. The leukocyte count a few weeks before death was 98,300, with a differential count of 12.8 per cent. neutrophilic myelocytes and transitionals, 38 per cent. neutrophilic polymorphonuclear leukocytes, 4.5 eosinophilic myelocytes, basophilic cells 2 per cent; large nongranular, 40.7 per cent., small nongranular 4 per cent. Seventeen normoblasts were seen while counting 1,450 leukocytes.

He described a typical eosinophil with peculiar fine, pink granules that are very scanty; also cells in every way like the large nongranular elements except that they contained coarse, spherical, basophil granules which were numerous. The author concludes from his observations on the origin of granular leukocytes in the human fetus, previously referred to [16] that such appearances indicate a reversion to fetal conditions, the large nongranular basophil cells being due to reversion of the granular myelocytes to undifferentiated leukoblasts, or to hyperplasia of the few such cells normally present in the adult marrow, with the resumption of the embryonic capacity for secreting granules.

In addition to the previously described cases of mixed leukemia, there are many cases of atypical leukemia recorded in the literature. I have picked out a few of them which may have some of the features of mixed leukemia, and may possibly fall into this classification.

In 1915, Krjukow [17] reported a case of acute microlymphoidocytic leukemia, in which there was hyperplasia of the follicles of the spleen

14. De Castello: Quoted by Herxheimer, Footnote 4.

15. Naegeli, O., and Pappenheim, A.: Quoted by Herxheimer, Footnote 4.

16. Browning, C.: A Case of Mixed-Cell Leukemia with a Short Account of Recent Views on Atypical Leukemias, Lancet **1**:507 (Jan.) 1905.

17. Krjukow, A.: Ueber einen Fall von akuter Microlymphoidozyten-Leukämie, Folia Haematol. **15**:328, 1915.

and lymph glands and a distinct development of myeloid tissue in the spleen. The patient improved so far as the leukemia was concerned but died of an intercurrent pneumonia.

Michaelis [18] found evidence of the differentiation from nongranular cells (probably immature lymphocytes) to fine granular types in the blood of a patient. The spleen showed large nongranular mononuclear and giant cells with similar types found in the bone marrow, liver and lymph glands.

Simon [19] reported a case with myeloid elements predominating in the blood at the onset, with decrease in the myeloid elements as death approached and a relative corresponding increase in lymphocytes.

A differential count on two of Wolff's [20] cases showed 78 per cent. nongranular cells, probably immature lymphocytes, with 17 per cent. myelocytes.

Klein and Steinhaus [21] report a count of 41,000 leukocytes, 66 per cent. of which were lymphocytes and 17 per cent. myelocytes. The myelocytes formed a greater part of various tumor masses throughout the body, but were not present in the spleen or the lymph glands.

In a case of Fowler's,[22] 50 per cent. of the cells were large nongranular types undoubtedly immature lymphocytes, with 12 per cent. myelocytes.

Wilkinson [23] reports a case which began as a typical myeloid leukemia, but later immature lymphocytes appeared in the blood. These increased in number as the disease continued and were quite numerous shortly before death. It is important to note that in this case "the peculiar feature of the blood was that lymphocytes were quite as numerous as myelocytes and there was every gradation between the two. All types of nucleated red cells were present." The last blood smear taken showed an amazing typical lymphocytemia though myelocytes were present.

Thus at first, there was a myelocytemia with lymphocytes in moderate proportion, while later a lymphocytemia with numerous myelocytes

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18. Michaelis, L.: Ueber einen der Gruppe der Leukämie-artigen Erkrankungen zugehörigen Fall, Ztschr. f. klin. Med. **45**:87, 1902.

19. Simon, C. E.: A Case of Myelogenous Leukemia with Severe Unusual Features (Absence of Eosinophilic Leukocytes), Am. J. M. Sc. **125**:984, 1913.

20. Wolff, A.: Ueber der Bedeutung der lymphoid Zelle bei der normalen Blutbildung und bei der Leukämie, Ztschr. f. klin. Med. **45**:385, 1902.

21. Klein and Steinhaus: Ueber das Chlorom., Centralbl. f. allg. Path. u. path. Anat. **15**:49, 1904.

22. Fowler, J. S.: On the Occurrence of a Form of Leukemia Intermediate in Type Between the Lymphatic and the Splenomedullary Forms, with Notes of a Case in a Child Five Years Old, Internat. Clin. **3**:217, 1903.

23. Wilkinson, R.: A Case of Leukemia with Change of Type in the Appearances of the Blood, Lancet **1**:1739 (Jan.) 1903.

present. It is apparent that the abnormal leukocytes present had undergone a complete change. This case resembles mine in that the myeloid leukemia predominated early while lymphocytic activity increased later. From the foregoing description, I believe Wilkinson's case became eventually one of true mixed leukemia.

DIFFERENTIAL DIAGNOSIS

Fabian, Naegeli and Schatiloff [6] define the acute lymphatic and myeloid types in their paper on leukemia. They also emphasize the point that in the beginning of acute lymphatic leukemia there is a certain small percentage of myelocytes in the blood which are crowded out of the bone marrow, due to the abnormal lymphatic proliferation there. The authors say these diminish rapidly as the disease progresses.

It is important to note in this regard that, although myelocytes may be found in the blood when any great demand is put on the bone marrow, promyelocytes and leukoblasts never appear unless there is a definite specific stimulation of the bone marrow, or extramedullary organs such as is found in myeloid leukemia.

The same can be said in reference to the lymphocytes in myelogenous leukemia, for here, although lymphocytes are found in the blood, the immature forms described by Naegeli are not found in the blood unless there is stimulation of the lymphatic tissue similar to that producing the activity of the myeloid tissue.

It is important that the diagnosis of leukemia should not depend on the blood findings alone. The case should be considered as a whole including the clinical picture as well as the histologic study of the various organs involved. This point was clearly shown in Pappenheim's case of myelogenous leukemia where the only changes present were in the bone marrow. Meyer, Heineke and Butterfield [24] reported a case of myelogenous leukemia with no changes in the bone marrow (both cases were referred to by Werzberg [25]).

Pappenheim,[26] Walz [27] and Dennig [28] have reported cases which hematologically were lymphatic leukemia, yet in these cases the spleen and lymph nodes were not involved, but the bone marrow showed some lymphocytes.

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24. Butterfield, E.; Heineke, A., and Meyer, E.: Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, Folia Haematol. **8**:337, 1909.

25. Werzberg, A.: Neue experimentelle Beiträge zur Frage der myeloiden Metaplasie, Virchow's Arch. f. path. Anat. **204**:272, 1911.

26. Pappenheim, A.: Zwei Fälle akuter grosszelliger Leukämie, Folia Haematol. **4**:301, 1907.

27. Walz: Quoted by von Domarus, Footnote 8.

28. Dennig, A.: Ueber akute Leukämie, München. med. Wchnschr. **47**:1297, 1900.

So the importance of a complete study of a case is evident. It was because Türk did not have any histologic studies to accompany his case of so-called mixed leukemia that he was criticized in making his diagnosis.

The importance of nucleoli as the distinguishing factor between the early types of lymphatic and myeloid cells has been greatly studied and discussed, but the present day viewpoint accepted by most hematologists is that they are worthless as a means of differentiation. Butterfield and Pappenheim [29] found that the number present varied so greatly that it was of no significance. Naegeli,[12] however, believes that myeloblasts can be differentiated from lymphoblasts by the number of nucleoli, there being more in the case of the myeloblasts.

With regard to the oxydase reaction, Pappenheim and Döhrer [9] conclude regarding it that "it does not indicate an absolutely unfailing histogenetic difference between two heterogenous cell races."

We cannot depend on the presence and character of azure granules in the cells as a sure means of differential diagnosis between myeloid and lymphoid cells. Hyneke [30] gives a comprehensive review of the literature up to 1912. Lippman, in an unpublished paper, reviews the literature up to 1922 and his conclusions are that, taken as a whole, azure granules are of no value in distinguishing between myeloid and lymphoid cells. However, he admits that the coarse, angular, purple granules described by Pappenheim as characteristic of the myeloid stem cell are only rarely found in lymphocytes and are numerically much less in the latter. The azure granules of lymphocytes are much finer and more reddish in color.

Hyneke, in his discussion of granules, states that he has found cells with both neutrophil and azurophil granules in an acidophilic cytoplasm. He disagrees with Gravitz and Pappenheim, whom he quotes, as saying that azure granules never occur except in a basic cytoplasm.

With the foregoing discussed points in mind, let us determine the classification of my case. The smears showed, as noted before, all stages of developing myeloid cells from the original stem cell of Pappenheim to the fully differentiated granular leukocyte. For this reason the case could not be classified under the heading of simple lymphatic leukemia. Naegeli might explain the presence of myelocytes through forcing out of bone marrow tissue into the blood, but I am sure that he would not feel that this argument would hold true where promyelocytes and leukoblasts were present, as well as stem cells with the typical myeloid type of granulation of Pappenheim.

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29. Pappenheim, A.: Bemerkungen über artliche Untershiede, usw., der lymphoiden Zellformen des Blutes, Folia Haematol. **9**:321, 1909.

30. Hyneke, K.: Fur Monoztytenfrage, Folia Haematol. **13**:345, 1912.

For practically the same reason the case could not be classified from the blood findings as simple myelogenous leukemia, for, as noted before, immature lymphocytes in various stages of development were present in all smears, even predominating in the later one. The blood picture in my case resembled very much that found by Türk in his first case. From the findings I cannot classify it as simple lymphatic or simple myelogenous leukemia, for there is a mixture of both types present, the latter predominating first and the former predominating later. So the blood findings indicate to me that my case is one of true mixed leukemia.

Histologic examination of the tissues does not allow me again to consider the case as a simple one of either type, but as a mixture of both, except in the case of the liver and the intestinal polypoid mass. The latter two, if considered alone, favor lymphatic leukemia, as the findings here are quite typical of this condition. This point, however, considered along with definite evidence of myeloid metaplasia in all the other organs examined, only emphasizes the fact that here we are dealing with a mixture of the two types.

Sections of all the other organs studied showed evidence of activity of both systems. Lymphoid metaplasia predominated in the spleen, yet there were areas where the myeloid activity was more in evidence. In these areas, the pulp also predominated. Myelocytes were even found in the areas of condensation of lymphocytes about some of the blood vessels, as described before. Some of these myelocytes had a small, dark-staining nucleus positively indistinguishable from the nuclei of some of the surrounding lymphocytes. The fact that the follicles had disappeared, and in some cases showed evidence of atrophy, as well as the fact that myeloid metaplasia was so much in evidence, make it impossible to classify this case as a pure lymphatic leukemia. Also the fact that there was a total increase in lymphatic tissue over that of a normal spleen, and the presence of large areas of concentration of lymphocytes, probably replacing the malpighian bodies, forbids placing it in the category of simple myelogenous leukemia.

The above statements hold true for the lymph glands as well as the spleen. Again, many of the myelocytes found in the lymph nodes had small dark nuclei, rich in chromatin, which were identical with those of adjacent lymphocytes. It would appear that they have a common origin, or better, that the myelocytes develop from the lymphocytes.

In reviewing the lung, kidney and pancreas findings the important fact to note is that both myeloid and lymphoid metaplasia was much in evidence in these organs. The local development of myelocytes and immature lymphocytes was common. The developing cells of both systems were mixed diffusely together with no definite arrangement and no evidence of separation of the two systems.

Because of this diffuse mixing together of lymphoid and myeloid elements in the various extramedullary organs, I have another strong reason for classifying my case as one of true mixed leukemia.

Myelocytes have been found in lymphoid organs in other instances, aside from cases of myelogenous or mixed leukemia.

Citron [31] and Fineman [32] reported cases where they found myeloblasts coming right out of the follicles in the lymph nodes.

MacCallum [33] would say that these cells were transplanted from the bone marrow and grew in the extramedullary organs. Naegeli [5] believed the same until recently, but now he admits that myeloid cells can develop from what he calls undifferentiated mesenchymal cells which occur about the blood vessels in extramedullary organs. However, he admits in his last textbook that these undifferentiated cells can develop into either lymphoid or myeloid types. He admits in this statement that there is a common mother cell of the two types under certain circumstances.

Meyer and Heineke [5] state that myeloid tissue in lymphatic organs does not arise from the lymphocytes in the follicles, but from an undifferentiated element similar to the lymphoid cells of bone marrow.

Sternberg [34] claims that the follicles and pulp strands can be enlarged in myelogenous leukemia so that the border between the follicles and the pulp is wiped out or indistinct. He has found myelocytes in the follicles.

Fabian, Naegeli and Schatiloff [6] state that study of the intermediate forms between the earliest types of immature cells and the adult cell is necessary in order to classify the unripe cells. For example, in the case of myeloid leukemia, intermediate forms between the myeloblasts and the myelocytes should be present in large numbers. They also mention the appearance of a large number of nucleated red blood cells in myeloid leukemia.

Using this as the criterion, it is evident that there was definite leukemic activity of both systems in my case.

The above citations, in correlation with the previously reviewed cases of mixed leukemia, in addition to my own case, are evidence enough, I believe, that myelocytes may develop along with lymphocytes in lymphoid organs, in spite of the fact that Naegeli and his followers insist that the two systems are entirely separate, and are never mixed or found together in the true sense of the word.

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31. Citron, J.: Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie, Folia Haematol. **20**:1, 1915.

32. Fineman, Solomon: A Study of Microlymphoidocytic Leukemia, Arch. Int. Med. **29**:168 (Feb.) 1922.

33. MacCallum, W. G.: Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1917.

34. Sternberg, C.: Leukosarkomatose und Myeloblastenleukämie, Beitr. z. path. Anat. u. z. allg. Path., Jena **61**:75, 1915.

Let us now consider some of the objections to the diagnosis of mixed leukemia which have been made by various men.

Naegeli,[7] of course, as well as his followers, insists that it is impossible to have a condition of mixed leukemia. They believe that the two systems, lymphatic and myeloid, are separate and distinct with a separate stem cell for each type from which the adult cells develop. They believe it is impossible to have a mixed form. The question whether or not there is a separate mother cell of the two types or whether they may develop from a single common mother cell will be discussed a little later in the paper.

Several objections or questions have been raised regarding previously reported cases of mixed leukemia.

Naegeli objects to Herz's case, claiming that the appearance of the myeloid cells was caused by displacement of marrow cells, due to sepsis, as an endocarditis was found at necropsy. Herz's answer to this objection has already been given in the previous discussion of his case. In regard to my own case there was no evidence of sepsis either from the clinical history, physical examination or at necropsy. Even if there had been, I do not believe that sepsis can explain the appearance of either the lymphoid or the myeloid metaplasia which was so very definite and prevalent in the spleen, lymph nodes, lungs, kidneys and pancreas.

Türk,[35] in 1907, reported two cases of septic disease with lymphemic blood findings. The first case showed 90 per cent. lymphocytes, and a diagnosis of lymphatic leukemia with secondary sepsis was made. Necropsy showed a septic endocarditis, and almost entire withering of the granulocytes in the bone marrow with replacement by lymphocytes. This was not considered a case of leukemia.

The second case showed leukocytosis with 62 per cent. lymphocytes. A diagnosis of lymphatic leukemia with secondary sepsis was made.

Erb[36] reports a case of lymphatic leukemia in which a secondary septicemia later developed. There were 91 per cent. lymphocytes and only 0.5 per cent. myelocytes. Tissue sections showed a lymphatic metaplasia in all the blood forming organs.

Eppenstein[37] discussed the question of acute leukemia with "Streptokokkensepsis" and reports several cases. He believes that the sepsis was the secondary invader. He refers to cases by many other authors including Vogedes, Fränkel, Jousfet, Holst, Ziegler and Jochman who report cases similar to his, with a positive blood culture. The path of

35. Türk, W.: Septische Erkrankungen bei Verkümmerung des Granulozytensystems, Wien. klin. Wchnschr. **20**:157, 1907.

36. Erb, W.: Septische Erkankungen und akute Leukämie, Deutsch. med. Wchnschr. **33**:833, 1907.

37. Eppenstein, H.: Akute Leukämie und Streptokokkensepsis, Deutsch. med. Wchnschr. **33**:1984, 1907.

entrance of the streptococcus could not be found, however, in Eppenstein's case. Even the tonsils, which are usually swollen in leukemia, were unchanged. The blood count in his case showed 96 per cent. lymphocytes. No myelocytes were found in the blood.

Naegeli, as quoted by Eppenstein, reports a case of chronic lymphatic leukemia where streptococcic sepsis appeared shortly before death. Although myelocytes appeared in the blood, no younger cells than these were found, and the myelocytes were present only in a very small percentage.

It is evident from the study of the preceding cases that sepsis alone will not produce a lymphatic metaplasia in the bone marrow, or myeloid metaplasia in the lymphoid organs where the opposite condition was primary and preexistent. In other words, add sepsis to an existing acute lymphatic leukemia and myeloid metaplasia will not appear in the extramedullary organs. Sepsis may cause the appearance of myelocytes in the blood in a case of acute lymphatic leukemia, but it never has been shown to produce myeloid metaplasia in the extramedullary organs.

Von Domarus [8] believes with Naegeli that one can get the same changes in a myeloid organ from sepsis as one can get in a myeloid leukemia, and quotes Meyer and Heineke as believing the same thing, and that it has been produced experimentally in animals. He refers here to the animal experiment of Rachzeh,[38] where lymphadenoid metaplasia of the bone marrow was observed. He also insists that the tissue reaction to bacterial toxins can be either myeloid or lymphatic in character.

However, the cases of sepsis and leukemia as reported in the literature which I have read do not coincide with these animal experiments. Blood and tissue changes somewhat leukemic in character produced in animals are very different from leukemia in human beings.

Another explanation which Naegeli gave for the appearance of the marrow cells in Herz's case was that it was agonal. I believe it is possible to have a few myelocytes thrown out into the blood, possibly as a compensatory effort on the part of the bone marrow, as death approaches, but the production of active metaplasia in the extramedullary organs is entirely unlikely.

Naegeli has also objected to the diagnosis of mixed leukemia, especially in the cases of Hirschfeld and Herxheimer, on the basis that the myeloid metaplasia, evidence of which was present in the blood smears and extramedullary organs, was due to displacement or transplantation of bone marrow tissue into the extramedullary organs, these myeloid cells having been forced out of the bone marrow because of the massive lymphatic infiltration with suppression of the myeloid activity there.

38. Rachzeh: Quoted by Von Domarus.

In speaking of Herxheimer's case, Sternberg [34] suggests that there was a local diminished resistance in the mediastinal tumor, possibly due to focal changes, so that myeloid activity could enter and take hold.

So far as I could determine, no proof was given to substantiate either one of these ideas, while, on the other hand, definite instances of myeloid metaplasia had been found in the extramedullary organs as discussed before. Instances of this have also been found in conditions other than that of mixed leukemia.

Butterfield [39] found cases of masses of myeloid cells in the extramedullary organs without hyperplasia of the bone marrow, and when he found myeloid tissue in the obliterated appendix and in granulation tissue, he had another good argument in favor of the local formation of myeloid cells, whether in the spleen, lymph glands or liver.

Werzberg [25] states that you may get myeloid metaplasia of the parts in cases of hyperplasia of lymph nodes. His assertion of the fact that lymph follicles are small and unseen and without germ centers in most cases of chronic myeloid leukemia does not indicate, however, that the lymphopoietic tissue was passive or was squeezed out or substituted by a myelopotent pulp tissue. But on the other hand, both pulp and follicles may react to the same poison by myeloid metaplasia or hyperplasia. It is evident that Naegeli's explanation need not always hold true.

Pappenheim [9] claims that the myeloblasts present are the result of the differentiation of lymphocytes coming from lymphoid tissue. In the same way he explains the presence of the lymphocytes as the result of a backward differentiation of myelocytes to a primitive stem cell, and a forward differentiation into the various stages of developing lymphocytes to the mature adult cell. However, he can only offer this explanation by assuming a polyvalent stem cell which, of course, he does.

In my case de-differentiation of lymphocytes back to the stem cell and then to myelocytes, or vice versa, is possible, but it seems to me there is more evidence of a direct formation of myelocytes from lymphocytes as indicated by the great similarity between the nuclei of some of the myelocytes and lymphocytes. This was very noticeable in the spleen, kidneys, lungs, pancreas and lymph glands. In the interacinar connective tissue of the pancreas many very small eosinophilic myelocytes were noted, where not only the nuclei were identical with those of the small lymphocyte, but the actual size of both of the cells was the same, indicating that many of these small lymphocytes in the tissue differentiated directly into myelocytes and developed eosinophilic granules without any change in the size of the cell occurring (Fig. 9 *g*).

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39. Butterfield, E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrüsen, Deutsch. Arch. f. klin. Med. **92**:336, 1907-1908.

Naegeli [15] explains the presence of the myeloblasts in Herxheimer's case as a compensatory activity of the stem cells of the leukocytes, following their oppression in the bone marrow. Similar observations have been cited by Fischer and Naegeli in lymphatic leukemia and in toxic anemia.

Ziegler [40] in his discussion of lymphatic and myelogenous leukemia states that an atrophy of one system means the hypertrophy of the other and vice versa. He says there must be a proliferation of the entire preformed tissue. But the fact that we have localized changes in leukemia speaks against Ziegler.

Hertz [41] has shown in his experiments on animals that leukocytic metaplasia may occur without formation of red blood cells, and that formation of leukocytes and the erythrocytes do not always run parallel. These experiments would indicate that myeloid metaplasia is not merely a compensatory phenomena on the part of nature.

The fact that there was so much evidence of activity of both systems in my case at all times, even though one or the other predominated slightly during the course of the disease, would make it seem illogical to explain the condition on the compensatory basis.

The use of roentgen ray and drugs in the treatment of some of the previously reported cases of mixed leukemia have been urged as an explanation by men who object to this diagnosis. Since my case received no roentgen-ray treatment and was given no medicine except simple tonics, it will not be necessary to discuss this objection.

The explanation of the findings in true mixed leukemia is so closely correlated with the origin of blood cells that a discussion of the former subject would be very incomplete without mentioning, at least briefly, the theories and views on the latter subject. Ehrlich [42] was the first one to lay down the laws of morphologic, biologic and genetic specificity of the white blood cells; namely, that lymphocytes originate in the lymphatic organs (spleen, lymph glands and adenoid tissue of the digestive tract) and the granular leukocytes along with red blood cells from the bone marrow. It has been shown since the time of Ehrlich that normal adipose tissue of the adult bone marrow can take on its embryologic function under pathologic conditions. Why, then, cannot the adult spleen, which is rich in myelogenetic tissue in intra-uterine life, assume its myelogenous function again under a similar pathologic condition?

40. Ziegler, R.: Experimentelle u. klinishe Untersuchungen über die Histogenese der myeloiden Leukämie, Jena, G. Fischer, 1906.

41. Hertz, R.: Zur Frage der experimentellen myeloischen, Milz Metaplasie, Ztschr. f. klin. Med. **71**:435, 1910.

42. Ehrlich, P., and Lazarus, A.: (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit) Anemia, New York, Rebman Company, 1910, p. 148.

Many clinicians and hematologists have discussed and tried to solve this question.

Hematologists are divided into two great schools, the dualists on one hand, who believe that there is a specific separate stem cell for the lymphocytes and the myelocytes, and, on the other hand, the monophyletists, who believe that, at least under certain conditions, lymphocytes and myelocytes may have a common "mother" or "stem" cell.

Among the chief exponents of the unitarian theory (monophyletic) as quoted by Downey and Fineman,[32] are Pappenheim,[43] Grawitz,[44] Weidenreich,[45] Maximow, Downey,[45] Ferrata, Du Toit, Arnold, Neumann, and Danchakoff.[46] Among the chief exponents of the dualists are Naegeli, Ehrlich, Stockard, Ziegler, Türk, Schridde, Fischer, Butterfield, Stillman, Meyer and Heineke.

Ehrlich's classification of blood cells forms the basis of the modern dualistic teachings and is practically accepted by the great majority of the clinicians today. I will first mention some of the points which the dualists offer in favor of their theory.

Ehrlich and the dualists insist that there is a marked contrast between myeloid and lymphatic tissues in their origin. They believe it is impossible to have a mixture of myeloid and lymphoid metaplasia, and that the lymphoblast and myeloblast are very different in appearance and can always be distinguished from one another.

Fabian, Naegeli and Schatilloff,[6] after an intensive study of many cases of lymphatic and myeloid leukemia, state that in no case did the lymphatic tissue become myeloid or vice versa. The findings in the organs as well as in the blood smears always showed the two types as distinct and separate.

Naegeli points to Herxheimer's case of apparent mixed leukemia as definite proof of the dualistic idea, in that here Herxheimer found a sharp distinction between the lymphocytic and myelocytic infiltrations in the different sections of the mediastinal tumor and the other organs studied.

Of course, as stated before, Naegeli[7] insists that there are no transitions between the myeloid and lymphatic systems. He explains the presence of myeloid metaplasia in the spleen and lymph nodes and the action of myeloid elements in the blood, by dividing the tissues of the spleen into myeloid and lymphoid elements. He classified the

43. Pappenheim, A.: Die Zellen der leukämischen myelose, Jena, G. Fischer, 1914.

44. Grawitz, E.: Klinische Pathologie des Blutes, Leipzig, Georg. Thieme, 1911.

45. Downey, H., and Weidenreich, F.: Ueber die Bildung der Lymphocyten in Lymphdrüsen und Milz, Arch. f. mikr. Anat. **80**:367, 1912.

46. Danchakoff, V.: Origin of the Blood Cells, Anat. Record **10**:397, 1916; Concerning the Conception of Potentialities in the Embryonic Cells, ibid. **10**: 415, 1916.

follicles of lymph nodes and spleen as being lymphoid, but the interfollicular tissue and pulp as being capable of producing myeloid cells.

Schridde [47] assumes that the endothelium of lymph vessels may give rise to lymphocytes, and that of blood vessels to myeloid tissue. However, Downey [48] has shown that lymphocytes are developed in great numbers in the spleen where there are no lymph vessels.

Naegeli,[7] in his latest textbook, still insists that there have been no proven cases where the transition from lymphoblasts to myeloblasts has ever occurred.

Referring to the large, indifferent nongranular cells, Butterfield [39] believes that one cannot tell whether they are myeloid or lymphoid in origin, but he adds that they must be different because of the widely separated localization in the tissues of the myeloid and lymphoid elements.

MacCallum [33] states that lymphoid and myeloid tissues are so specific that they are never mixed. He insists that examples of abnormal metaplasia are due to transplantation of cells which then grow in their new locations.

The unitarians also have evidence for their theory. Pappenheim,[49] in 1908, assumed a common stem cell for both lymphocytes and myelocytes and says it is ubiquitous in all hematopoietic tissue. It may be the germ center cell of lymphatic tissue or the primary stem cell of myelogenous tissue. The presence of these stem cells may explain the origin of myeloid metaplasia of the splenic pulp and lymphoid metaplasia of the bone marrow. From them, by proliferation and differentiation, we may get lymphocytes or myelocytes, lymphatic or myeloid tissue, depending on whether the irritation is lymph or myeloplastic.

Pappenheim,[26] in a study of two cases of acute large cell leukemia, states that both cases point to the morphologic type of large lymphocyte of Ehrlich as an indifferent multipotent lymphoblastic and myeloblastic stem cell. Pappenheim concludes that, if the dualists are right, the large lymphocyte found in the first case can only be the stem cell of the myeloblast; and in the second case with many small lymphocytes, there must be a mixed leukemia; that is, a myeloidlymphadenoid leukemia; and in the former case a lymphadenoidmyeloid leukemia. They believe that in one case there is atrophy of lymphadenoid tissue and in the other suppression of myeloid production.

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47. Schridde, H.: Die embryonale Blutbildung, Erwiderung an Herrn Prof. A. Maximow, Zentralbl. f. allg. Path. u. path. Anat. **20**:433, 1909.

48. Downey, H.: On the Development of Lymphocytes in Lymph Nodes and Spleen, Tr. Minn. Pathol. Soc. 1912, 1914.

49. Pappenheim, A., and Hirschfeld, H.: Ueber akute myeloide und lymphadenoide, makrolymphoidcytäre Leukämie an der Hand von zwei vershiedenem Fällen, Folia Haematol. **5**:347, 1908.

Citron,[31] in 1915, reported a case of leukemia where the blood showed a definite myelogenous picture with a normal bone marrow. Citron's conclusion was that the micromyeloblastic cells of the blood were being generated in the follicles and interfollicular tissue of the lymph nodes and spleen, and that these cells were passing from the follicles into the blood stream.

Fineman [32] presented a case of acute micromyeloblastic leukemia where a lymph node was obtained in vivo, the study of which showed "atypical cells proliferating in great numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles, and in the germ centers of the lymph follicles. Transition forms between the connective tissue cells of the capsule and these atypical cells, as well as between lymphocytes and the atypical cells, were present in the capsule. In the interfollicular tissue, as well as in the follicles, and even in the germinal centers, transition forms between these atypical cells and reticulum and lymphocytes were also present. These atypical cells form the majority of the cells of the parenchyma." In conclusion, he states that the myeloblasts and micromyeloblasts of the blood were coming from these atypical cells found in the organs.

These two cases (Citron and Fineman) are of utmost significance, in that they are the first ones on record which would seem to prove that the dualistic doctrine of the origin of white blood cells does not always hold true.

Werzberg,[33] in studies on myeloid metaplasia, found in his cases all transitional stages from the large lymphocyte to the fully differentiated polymorphonuclear cell. He found intensive hyperplasia of splenic follicles with rarefication of splenic pulp which was undergoing myeloid metaplasia. The large lymphocytes of the bone marrow were identical in structure with those of the germ centers and the pulp of the spleen.

Downey's [45] investigations show clearly that the lymphocyte is not a fixed and fully differentiated cell which is incapable of further differentiation, as was claimed by Ehrlich. He has seen it develop into a large mononuclear macrophage as well as into plasma or mast cells. He states that the lymphocyte is really a primitive, rather indifferent cell whose morphologic appearance depends on the stage of development and the particular function which it happens to be performing at the time. It is capable of differentiating into various types of granular leukocytes. Downey does not recognize the term "lymphoblast" used so much by Naegeli in his discription of the large mononuclear cell of the germ centers. The large lymphocytes of the germ centers, which Downey studied, did not conform to the description given by Naegeli and others. Downey has shown that there is not a particular type of lymphocyte only found in the germ centers, but that the same cell

occurs also in the interfollicular tissue or in the splenic pulp; in fact, everywhere in the adenoid tissue, and that the lymphocytes have a twofold origin; namely, from the reticulum, and from large mononuclears which came from the reticulum, or from lymphocytes.

In spite of the apparent antagonistic views of the unitarians and dualists, concessions have been made on both sides. Naegeli, in the last edition of his textbook, admits that the mesenchyme cell found in the neighborhood of the blood vessels may differentiate under pathologic and physiologic conditions in both directions. In this respect, at least, he is a unitarian. On the other hand, Pappenheim [9] stated that at present a morphologic difference between lymphatic and myelogenous lymphoid cells must be admitted, although it has not been proved definitely that development cannot occur from one to the other, or that a myeloid cell in the blood must always be derived from myeloid tissue and a lymphocyte from lymphatic tissue.

The formation of lymphocytes from myeloid tissue can be explained by the dualists on the basis of substitution.

Some men hold an intermediate view between the unitarian and dualistic. Hirschfeld [50] believes the "golden" middle position between the dualistic of Ehrlich and the absolute unitarian ideas of younger authors to be the best. The stem cells of the lymphatic and myeloid tissues are morphologically the same but are different in their function and further cytologic differentiation.

Browning [16] believes leukemia to be a sarcoma of the blood with reversion to the embryonic type of cell; that is, reversion to the condition existing in the marrow of fetal life. The case which he gives as an example has already been discussed. As to the origin of blood cells, his observations on the findings in the human fetus indicate that eosinophilic and neutrophilic leukocytes arise from the mitotic division of large mononuclear granular cells lying in the loose connective tissue. Large nongranular basophil cells are the result of reversion of granular myelocytes to the nongranular "premyelocyte" or leukoblast or so-called "stem" cell stage. He states that Muir agrees with him.

Danchakoff [46] believes that the stem cell, or so-called large lymphocyte, appears first during the dissociation of the blood islands and is a young undifferentiated cell which differentiates according to given environmental conditions. She states that the fact that stem cells, as stem cells, keep their morphologic structure so tenaciously under the most varied condition, and that only their products differ, seems to speak strongly for the existence of a single cell identical in the hematopoietic organs.

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50. Hirschfeld, H.: Die unitarische und die dualistische Auffassung über die Histopathologie der Leukämien, Folia Haematol. **6**:382, 1908.

Observations in my own case point toward the unitarian idea as being the correct one for the following reasons: First, that from a study of the blood smear there seems to be a common stem cell for developing lymphoid and myeloid cells, as a series of both types could be found, starting with this apparently common stem cell. Second, this same common stem cell could be found in the tissues in the spleen, lymph nodes, kidney, lungs and pancreas mixed in with developing myeloid and lymphoid cells. Third, that many of the young eosinophilic myelocytes as well as the adult eosinophils had nuclei which were identical with adjacent lymphocytes. These myelocytes were not the type found in normal marrow. It seems logical to deduct that they differentiated directly from the small lymphocyte. Some of the granules of the young eosinophils were still very young, indicated by their basophilic staining. Fourth, that differentiating lymphocytes and myelocytes were found diffusely intermixed in the tissues away from the neighborhood of blood vessels in most of the organs studied.

The above findings, in my opinion, could not be as satisfactorily explained on any other theory except that held by the unitarians.

Again, if there is a separate stem cell for the myelocytes as Naegeli claims, I should have found more myelocytes in the areas of cell infiltration in the liver. If the so-called "stem" cells which were present are myeloblasts as Naegeli would call them, why do I not find more myelocytes here as I did elsewhere? It is evident that the dualistic theory cannot explain the condition found in the liver satisfactorily in correlation with the findings in the other organs.

In concluding the discussion of the subject of mixed leukemia, I should like briefly to compare my case with those previously reported. The blood findings apparently resemble that found by Türk in his first case. In both cases the myeloid element predominated primarily, while later lymphoid activity was slightly more pronounced. This is also true of Wilkinson's case.

Hirschfeld [2] found myeloid metaplasia in the splenic pulp and lymph glands, along with lymphadenoid metaplasia in the bone marrow. He showed a continuous series of transitional forms leading from the typical acute lymphocytic leukemia to the acute mixed cell type, such as were seen in my case.

In the cases of Herxheimer and Herz, the lymphatic hyperplasia was primary, with the myeloid activity developing later. Herz's observations of the myeloid changes in the spleen and lymph nodes were similar to my case, except that there seemed to be more of a separation between the two types in the case of Herz, while mine, as mentioned before, showed a diffuse mixture of the two.

Herxheimer also emphasized the fact that there seemed to be a distinct separation of the areas of myeloid and lymphoid activity, and

therefore called his case one of combined lymphatic and myeloid leukemia rather than a true mixed type.

The cases of Hirschfeld and my own seem to be the only ones reported in the literature which show histologic study to support the blood findings in making the diagnosis of true mixed leukemia.

Before concluding this paper, I wish to correlate some of the more important ideas regarding mixed leukemia, and discuss very briefly the subject itself. I have already discussed the objections which certain hematologists make against the diagnosis of true mixed leukemia, so I will limit myself now especially to the reasons why some hematologists believe it is possible that a form of true mixed leukemia can exist.

Let me repeat again the requirements which von Domarus and Browning have stated are necessary in order to make the above diagnosis; namely, that one must find in the histologic preparations hyperplasia of both myeloid and lymphatic tissue next to each other and occurring at the same time. Von Domarus quotes Hirschfeld's case as the only one of true mixed leukemia that has been reported. However, at the time when this statement was made, Herxheimer's case had not appeared in the literature.

The various men who have reported cases which they believe to be true combined or mixed leukemia, explain the cause of the simultaneous activity of the two systems in many ways.

Browning feels that the mixed cell picture is due, first, to the reversion of the myeloid cells to the embryonic nongranular type; second, a reaction or mechanical disturbance of the myeloid tissue, owing to lymphoid hyperplasia, resulting in the passage of myelocytes into the circulation. He feels that the toxins causing leukemia vary in their action and may give mixed types. However, he carefully avoids making any statement as to whether he believes his case to be one of true mixed leukemia.

Hirschfeld felt that the fact that his case showed undisputable evidence of simultaneous activity of both systems was enough evidence on which to make a diagnosis of mixed leukemia. He offers no opinions as to how the mixed cell picture is brought about.

Herz calls his case one of mixed leukemia, yet he states in his discussion that the hyperplasia of the lymphadenoid tissue within the myeloid bone marrow, and the hyperplasia of the lymph follicles and pulp strands in the lymph glands, to the complete loss of structure, does not necessarily signify an exceptional increase of the lymphadenoid tissue components of a myeloid leukemia, but is a disease of the lymphatic system itself along with a similar disease of the myeloid tissue; that is, a lymphatic leukemia with a myeloid leukemia. In another place he says, "the fact that, along with many lymphocytes, an important

number of the elements of the myeloid tissue were present in the blood, proves there must be a disease of both types of tissue; that is, a mixed leukemia." He suggests that the same poison or toxin may act on the one tissue and later on the other, or there may be two different toxins, and further that the infectious toxic agent may cause a reaction of both tissues at the same time, or after an exhaustion of one system, call forth an activity of the other. I cannot tell whether Herz believes his case to be one of combined or mixed leukemia; that is, whether he makes a distinction between the two words.

Herxheimer, however, leaves no doubt in one's mind in regard to his belief that his case is one of a combined leukemia; that is, an activity of both the lymphatic and myeloid systems with a distinct separation of the two types throughout. He emphasizes this fact in the discussion of his case, stating that nowhere was there evidence of fusion of myeloid and lymphoid elements. He believes this observation to be a strong point in favor of the dualistic theory, and cites his case as a good example of one showing that the two forms of leukemia can go on together and yet be distinct. I believe that both Herz and Herxheimer are dualists at heart. Herxheimer concludes that his case speaks against any transitional forms between the two types of cells, and says that the second one can only exist in the sense of a combination like carcinoma and sarcoma in the same individual without carcinomatous cells changing into sarcomatous cell.

In regard to my own case, as well as those before mentioned, it is evident that it meets all the requirements laid down by von Domarus and Browning in order to be called true mixed leukemia. It differs from the cases of Herz and Herxheimer in that I found a definite fusion and mixture of both systems, most marked in the spleen, lymph glands, alveolar walls of the lungs, interacinar tissue of the pancreas and in the kidneys. Although the presence of the myelocytes in the extramedullary organs may be explained on the bases of de-differentiation of the lymphocytes back to the stem cells and then to the myelocytes, it seems that there is more evidence of a direct formation of myelocytes from lymphocytes as has already been discussed in detail. It is important to note again that these myelocytes were present in the interfollicular tissue, not just around the blood vessels where Naegeli believes that they are only found. It is evident that the findings in Hirschfeld's case, and my own, speak very strongly against the dualistic theory of Ehrlich and his followers, and favors the unitarian idea in the sense that there is apparently a common stem cell for both types of developing cells. But also in my case there is evidence of a direct transition from lymphocytes to myelocytes without going through the stage of the stem cell.

As to the cause of the picture of mixed leukemia, I probably can offer no new suggestions, at least no better than have already been given. The fact that there may be two toxins present, one stimulating the lymphatic system, the other stimulating the myeloid system, is possible, but it seems more likely, at least in my case, that there was only one toxin which excited an abnormal activity of both systems, because of the fusion of the products of activity of the two systems.

It is possible that there may be only one kind of acute leukemia, at least in a hemomorphologic sense, and that the lymphoid cells of acute lymphatic and myeloid leukemia are isomorphous. No evidence has been given, however, to confirm this idea.

Werzberg [25] believes that leukemia, as a whole, is after all, a true endogenous disease, whose direct cause is not one of a common excitant or mysterious poison, but a one sided cellular disturbance that attacks the normal organs.

I do not believe we will find the explanation of true mixed leukemia until we determine the cause of simple leukemia. The question must still remain open, with a hope that future investigations may give us more definite information on this peculiar malady of mankind.

SUMMARY

1. Report of a case of acute leukemia, showing definite evidence in the blood smears as well as in the histologic study of the tissues of activity of both the myeloid and lymphoid systems.

2. Cells representing the various stages in the development of lymphocytes and granular leukocytes from the original "mother" or "stem" cells to the adult types could be found in the blood smears.

3. Immature lymphocytes and myelocytes were found mixed together in the pancreas, kidneys and lung in the areas of leukemic infiltration.

4. Myeloid and lymphoid metaplasia was noted in the spleen and lymph nodes, with a slight predominance of the latter. Immature cells of both types were diffusely arranged with no evidence of segregation.

5. There was evidence of local development of myelocytes from lymphocytes in the tissues.

6. Many of the immature myelocytes, particularly the "stem" cells, showed the typical coarse "myeloid azure granulation of Pappenheim."

7. Histologic studies showed a similar, simultaneous hyperplasia of lymphatic and myeloid tissue next to each other, which are the necessary findings required by von Domarus and Browning, in order to give it the name of the true mixed leukemia.

8. There was no evidence of sepsis found at necropsy.

9. There was apparently a single toxin stimulating both systems into a leukemic activity.

10. The findings in the blood smears, as well as in the histologic study of the organs, pointed to the unitarian theory of the origin of blood cells as being the correct one, at least in certain pathologic conditions.

11. No new observations were made relative to the real cause of the simple or mixed form of leukemia.

12. Another case of a true mixed form of leukemia is added to a small number of previously reported cases.

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A HITHERTO UNDESCRIBED FORM OF VALVULAR AND MURAL ENDOCARDITIS *

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In previous communications,[1] cases of endocarditis were classified as rheumatic, syphilitic, bacterial—acute and subacute—and indeterminate. The latter term was introduced to designate certain cases which do not fall into the category of any of the well-recognized groups of endocarditis, and the etiology of which is not yet established. The term is used to include (a) the cases of so-called "terminal" or "cachectic" endocarditis, occurring at the close of chronic diseases such as carcinoma, tuberculosis, nephritis, and leukemia, and (*b*) cases of "atypical verrucous endocarditis." The purpose of the present communication is to discuss the cases included in the latter group, which we believe represent a hitherto undescribed form of endocarditis.

We are at the present time reporting the study of four cases, clinical observations of which were supplemented by postmortem examinations. In each instance, there were peculiar valvular and mural lesions, which differed in morphology and localization from those generally encountered in subacute bacterial, rheumatic and other forms of endocarditis. The vegetations were free from demonstrable micro-organisms, and attempts to grow bacteria from the blood proved unsuccessful, despite the employment of methods which gave positive results in the great majority of cases of subacute anhemolytic streptococcus (and *Bacillus influenzae*) endocarditis. Because of the unusual character of the endocardial lesions and their verrucous appearance, these cases were designated "atypical verrucous endocarditis." When this form of endocarditis is better understood, a more satisfactory terminology will doubtless be introduced.

REPORT OF CASES

CASE 1.—*History.*—S. H., a woman, married, aged 24, admitted to the Mount Sinai Hospital, Jan. 21, 1922, and whose family history was unimportant, three years prior to admission to the hospital had an attack of polyarthritis, during which her ankles, knees, wrists, and elbows became painful and swollen. She states that she lost 60 pounds (27.2 kg.) during 1921.

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* Read in abstract before the Association of American Physicians, Atlantic City, N. J., May 1, 1923.

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1. Libman, Emanuel: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923; Brit. M. J. **2**:304 (Aug. 28) 1920.

Her general health was good until six weeks before admission, when she developed "sticking" precordial pain, which was intensified on deep inspiration. Two weeks later, she had a chill, followed by fever, and her ankles, knees, wrists, elbows and shoulder joints became swollen and tender. At the same time, her face became greatly swollen, and the urine was scanty. She experienced "drawing" pains in the left lumbar region, and the blood pressure was elevated. A week before admission, she developed sore throat. The edema of the face diminished, but the articular and precordial pains persisted.

Physical Examination.—The patient was poorly nourished and acutely ill, and had a temperature of 103.4 F. There were present slight puffiness and pallor of the face. Petechiae were present in the conjunctival mucous membrane of both lower lids and on the anterior aspect of the thorax and both sides of the neck. The pupils were equal and reacted promptly to light. The tonsils were moderately enlarged and congested. The respirations were shallow and somewhat accelerated, but not labored. The lungs were negative. The heart was not enlarged; the action was rapid but regular. The first sound at the apex was increased in intensity. A systolic murmur was audible over the entire precordium and in the left axilla. The second pulmonic sound was accentuated. The pulse rate was 96, respiration rate 36, and the blood pressure, 145 systolic, 90 diastolic. The abdomen was distended and held rigidly, and there were pain and tenderness in the left hypochondrium. Neither the liver nor the spleen was palpable. The left elbow and both ankle joints were swollen and tender, but the overlying skin was not reddened. The right elbow joint, both wrist joints and the left knee joint were tender, but there was neither swelling nor redness. Over the extensor surface of both forearms, the skin showed erythema and induration, and there was both cutaneous and muscular tenderness (dermatomyositis). The deep and superficial reflexes were active.

Course.—January 23: The pulse was 120; respiration, 44. The petechiae were fading. The urine was reduced in quantity and contained a heavy trace of albumin and a few hyaline casts. The blood showed no nitrogen retention (compare figures below).

January 24: Over the ramus of the left mandible, there was a distinct white-centered petechia. The patient had been having frequent attacks of pain in the left hypochondrium.

January 25: The fundi were normal.

January 27: The dermatomyositis had disappeared.

January 29: Both elbow joints were tender. There were dulness and diminished breathing at the left base posteriorly, below the level of the angle of the scapula.

January 30: The joint pains had improved.

February 4: The first to the fourth left metacarpophalangeal joints, inclusive, were painful and tender, but although there was practically no periarticular swelling, the skin overlying the dorsal aspect of the joints was of a peculiar red color, unlike that seen over the seat of typical rheumatic arthritis.

February 7: There was now dulness and diminished breathing over both lower lobes, posteriorly.

February 8: The pulse was 116; respiration, 28. A to-and-from pericardial friction rub was audible in the region of the apex of the heart and over the left fourth interspace just lateral to the sternum. The patient complained of "sticking" precordial pain similar to that experienced at the onset of her illness.

February 14: The friction rub had disappeared. Diffuse moist râles were audible over both lungs and there was profuse seromucoid expectoration.

February 17: The precordial pain, which had disappeared for a time, returned. The temperature rose to 104 F., and the pulse rate to 140.

February 19: Thoracentesis on the right side yielded 250 c.c. of clear fluid, and on the left side 20 c.c. of blood-tinged fluid. The fluid from both sides was sterile. The general condition of the patient was growing progressively worse.

February 21: A fresh crop of white-centered petechiae appeared over both sides of the neck and on the anterior aspect of the chest. The temperature dropped to 98.8 F., but the pulse rate remained accelerated, and was now 120.

February 22: The neck was rigid, and the Kernig sign was positive, bilaterally. Chemical examination of the blood now showed definite nitrogen rention. Blood cultures were persistently negative.

March 1: The abdomen showed signs of fluid and both lower extremities were edematous.

March 5: Numerous fresh petechiae appeared in the palpebral conjunctiva and on the skin of the neck and thorax.

March 7: There was a small exudate in the fundus of the right eye on the nasal side of the disk.

March 10: A bed sore appeared over the sacrum. There were signs of bilateral pleural effusion and ascites. The lower extremities and vulva were greatly swollen.

March 13: The patient had been having attacks of severe precordial pain radiating to the back and left shoulder. A few fresh petechiae had appeared in the left lower palpebral conjunctiva. The temperature for the last two weeks ranged around 100.

March 19: The patient began to vomit bloody fluid.

March 22: The breathing was labored and the breath uremic. Albuminuria become more marked. Paracentesis abdominis yielded 1,500 c.c. of clear straw-colored fluid.

March 24: A fresh crop of petechiae appeared.

March 31: Ascites and edema were increasing. Paracentesis was performed. The daily urinary output varied between 300 and 600 c.c. The precordial pain persisted and morphin was frequently required for its relief.

April 4: The patient had a generalized convulsion, following which she remained comatose for some time. When consciousness returned, she complained of severe precordial pain.

April 6: A second convulsion, ushered in by pain in the right arm, was followed by pulmonary edema.

April 13: Paracentesis abdominis yielded 5 liters of clear straw-colored fluid.

April 29: The ascitic effusion reaccumulated and the subcutaneous edema spread to the abdominal wall. A new crop of petechiae and purpuric spots was present.

May 3: A diffuse herpetic eruption (herpes zoster) appeared on the left side just below the breast and the angle of the scapula. The edema now became generalized. The precordial friction rub was again audible.

May 23: The pulse rate varied between 80 and 100. No new murmurs appeared. From time to time, the patient complained of severe epigastric and precordial pain.

May 29: The oliguria became more marked, and the general condition was growing progressively worse.

May 31: The patient suddenly became dyspneic and cyanotic, with pulse more rapid and irregular. She grew stuporous and died.

Temperature Curve.—January 21: The range was from 101 to 103.6 F.

January 22-27: The temperature gradually came down in remittent fashion to 101.2 F.

January 28-February 3: The temperature was not over 101 F. at any time. At the end of the week, it was down to 99.6 F.

February 4-10: The temperature was irregular, remittent and gradually higher until it reached 103.8 F., February 10.

February 11-17: The temperature was irregular, ranging from as low as 99.6 F., to as high as 104 F. (February 17).

February 18: The temperature ranged from 100 to 104.4 F.

February 19: The temperature remained near 104 F.

February 20: There was a sharp drop to 98 F.

February 21-25: The temperature was irregular, ranging from 97.2 and 98 to 100 and 101 F.

February 26-27: The temperature was 101 F.

February 28-March 23: The temperature was never above 100.4 F., usually at 99 or 100 F.

March 24: The range was from 99 to 101.8 F.

March 25-April 5: The temperature was never over 101 F., and was sometimes as low as 97 F.

April 6-14: The temperature was not over 99 F., excepting for a rise on the last day to 100.6 F.

April 15-May 3: The temperature was very low, never over 99.8 F., often 98 F.

May 4-May 31: At times, the temperature was as low as 96.4 F. or 97 F., usually not over 99 F., except for a rise to 100.6 F., May 4, and 101 F., May 21.

Respiration.—January 21-31, the rate was usually about 36. Later, it varied from 24 to 28, occasionally rising to 32 or 36. After February 18, it increased to 40, remaining near that figure until after March 18, when it dropped to a figure usually varying between 24 and 28, sometimes dropping as low as 20.

Pulse Rate.—January 21-27, the rate was usually 120. It gradually decreased, and after February 1, it ranged from 84 to 100. With sharp rises of temperature, it increased, reaching as high as 142, February 19, and 154, February 20. After February 26, it was usually 110-132, even though the temperature did not rise above 101 F.

Amounts of Urine.—At first, the figures varied between 700 and 2,200 c.c.; after February 11, from 600 to 750 c.c. The amount remained about the same after this time, at times increasing to 900 c.c., or decreasing to 300 or even 115 c.c. After March 25, the amount never exceeded 625, and often was as low as 250 or 150 c.c.

Laboratory Examinations.—These are given in Table 1.

Necropsy (eighteen hours after death).—The body was that of a well developed, emaciated young woman, showing marked pallor of the skin and mucous membranes. No petechiae were present. There was marked pitting edema of both lower extremities extending as far as the calves. There were several decubitus ulcers, the largest of which was 3.0 cm. in diameter. The base of the ulcers was covered with a dirty greenish exudate. The skin over the left fifth and sixth intercostal spaces both anteriorly and posteriorly showed desquamation and pigmentation (residue of recent herpes zoster).

The heart was moderately enlarged, weighing 360 gm. The pericardial membranes were universally thickened as a result of organizing fibrinous pericarditis, and there were extensive friable adhesions between the visceral and parietal layers, which almost completely obliterated the pericardial sac. The adhesions over the anterior aspect of the left ventricle were quite fibrous and were firmer than elsewhere. There was no effusion. There were rather firm, fibrous adhesions binding the parietal layer of the pericardium to the adjacent pleura on the left side. The tricuspid valve showed a discontinuous fibrous thickening representing a healed organic lesion. There were several minute healing translucent vegetations along the line of closure. The pulmonary valve was negative. The mitral orifice admitted three finger tips. The mitral valve showed a fairly continous fibrous thickening involving the closure line and free

edge, pointing to a previous attack of endocarditis. Along the line of closure, extending in places to the free edge, there was a row of rather firm translucent grayish verrucous vegetations (Fig. 1). A part of some of these was yellowish gray in color and opaque.

The endocardium over the upper part of both papillary muscles of the left ventricle and the intervening mural endocardium was the seat of an inflammatory process. There had also been an extension of the endocarditic process from the

TABLE 1.—*Laboratory Examinations* *

Urine

Date	Amount, C.c.	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic
1/22	...	Cloudy	Acid	1.018	++	0	Hyaline casts; no erythrocytes
2/27	...	Cloudy	Alkaline	1.020	++	0	Numerous leukocytes and a few erythrocytes
3/10	400	Cloudy	Alkaline	1.022	+	0	Numerous leukocytes and erythrocytes, and a few granular casts
4/11	350	Cloudy	Alkaline	1.014	++++	0	A few erythrocytes
4/19	400	Cloudy	Alkaline	1.012	++++	0	A few leukocytes and hyaline casts; no erythrocytes
5/22	...	Alkaline	.....	1.020	+++	0	Hyaline and granular casts; numerous erythrocytes
5/29	...	Turbid	Alkaline	1.010	++	0	Numerous erythrocytes and leukocytes

Blood Chemistry

Date	Urea N, Mg. per Hundred C.c.	Nonprotein N, Mg. per Hundred C.c.	Uric Acid, Mg. per Hundred C.c.	Creatinin, Mg. per Hundred C.c.
1/23	22.4	46.7	5.0	2.0
2/17	25.2	50.9	3.3	1.4
2/22	64.4	104.2	4.2	2.8
4/24	49.0	71.6	...	...

Phenolsulphonephthalein Test (1 C.c. Injected)

1/24	50 per cent. recovered in 2 hours
1/25	45 per cent. recovered in 2 hours
3/20	30 per cent. recovered in 2 hours
4/ 2	5 per cent. recovered in 2 hours

Blood Count

	Date				
	1/22	2/12	3/6	3/31	4/29
Red blood cells	5,400,000	2,936,000	2,088,000	.....	2,500,000
Hemoglobin, per cent.	84	56	34	39	38
Color index	0.86	0.96	0.83	....	0.76
White blood cells	6,500	5,400	13,400	21,600	....
Polymorphonuclear neutrophils, per cent.	84.0	67.5	79.0	72	....
Eosinophils, per cent.	1.0	2.0	0.5	0	....
Basophils, per cent.	0	1.0	0.5	1	....
Lymphocytes, per cent.	13.0	23.0	19.0	25	....
Monocytes, per cent.	2.0	5.5	1.0	2	....
Neutrophilic myelocytes, per cent.	0	0.5	0	0	....
Plasma cells, per cent.	0	0.5	0	0	....
Platelets	....	192,000	240,000	....	....
Coagulation time	....	12 min.	10 min.	....	....
Bleeding time	....	2 min.	4 min.	....	....
Capillary resistance test	....	Neg.	Neg.	....	....
Clot retraction	....	Present	Present	....	....

* The Wassermann reaction of the blood was negative. Blood cultures were made four times (January 22 and 28, and February 1 and 22); the mediums used were bouillon and glucose bouillon flasks, and plain agar and glucose agar plates; all were negative.

ventricular aspect of the posterior cusp of the mitral valve downward along the mural endocardium of the ventricle toward the tip of the posterior papillary muscle. The surface in these areas was covered by extensive flat grayish brown and yellowish patches of firm but friable deposit. The lesions on the mural endocardium just lateral to the posterior papillary muscle were grayish and more fibrous than elsewhere. Near the apex of the left ventricle, there was a

flat area of mural endocarditis, measuring 2.5 by 3.0 cm., irregular in outline and sharply demarcated from the surrounding healthy endocardium (Fig. 1). The patch presented a lusterless irregularly fissured surface, which was a mottled, grayish and reddish brown. On cut section, the deeper layers had a grayish translucent appearance, and delicate fibrous strands extended into the subjacent myocardium. The aortic valve showed a few minute firm translucent vegetations. The myocardium was pale and brownish, showing numerous fine grayish streaks. The coronary arteries and aorta showed a slight degree of atherosclerosis.

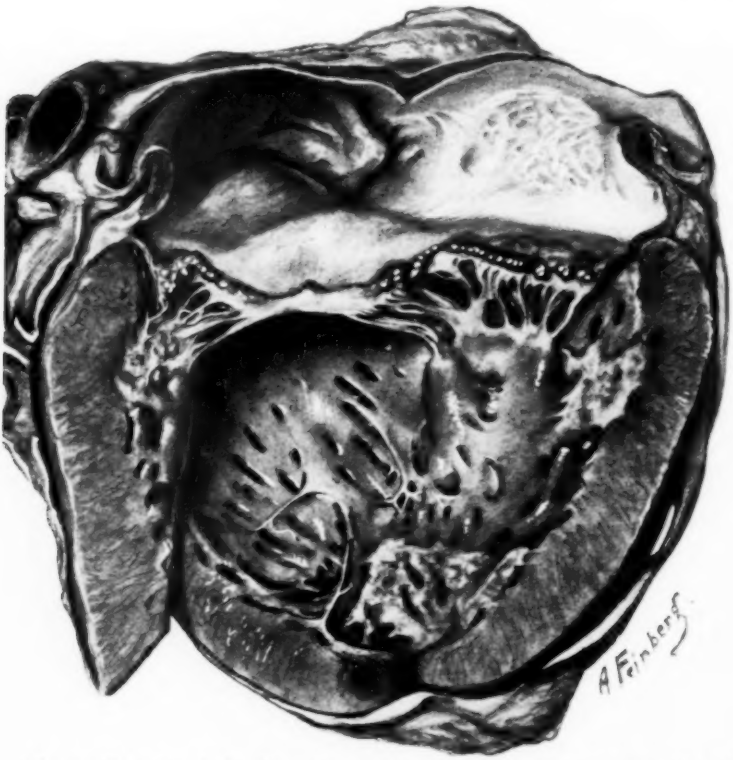

Fig. 1 (Case 1).—Left side of heart. Verrucous vegetations along line of closure of mitral valve extending in places to the free edge. There are areas of endocarditis on papillary endocardium and adjacent mural endocardium and an isolated patch of mural endocarditis in region of apex of ventricle. Universal healing fibrinous pericarditis is present.

In the lungs, there were friable adhesions between the visceral and parietal pleura on both sides, especially marked in the region of the diaphragm. These adhesions were the result of the organizing exudate of recent fibrinous pleurisy. The left pleural cavity contained about 250 c.c. of clear fluid. There were numerous minute subpleural hemorrhages. Both lungs showed marked congestion and edema, but no areas of consolidation.

The abdomen was markedly distended, the umbilicus being flush with the surface. The peritoneal cavity contained 4 liters of clear yellowish ascitic fluid. There was no evidence of peritoneal inflammation.

The liver was shrunken, weighing 780 gm. The capsule was wrinkled and the parenchyma was pale, brownish and cloudy, and showed marked chronic congestion.

The spleen was small, weighing 80 gm. The organ was of a rather firm elastic consistency. The malpighian bodies were small and the pulp showed congestion. Near one of the poles was a small depression, which on cut section was found to be due to a healed infarct.

In the kidneys, the capsule of the right stripped with difficulty, revealing a granular and nodular surface. The elevated areas was a pinkish gray, whereas the depressed areas were a deep red. On cut section, the cortex was somewhat narrower than normally, having a thickness of from 0.4 to 0.5 mm. The cortical tissue was pale and turbid, a mottled pink and gray. These striations were indistinct, and the glomeruli were not prominent. The left kidney showed in addition to the changes seen in the right kidney, a number of abscesses in both cortex and medulla, their diameter varying from 0.3 to 1.5 cm. Cultures of the pus from the abscesses showed *Staphylococcus aureus*. The pelves, ureters, bladder, uterus and adnexa were negative.

Microscopic Examination.—Examination of the myocardium and pericardium revealed an organizing fibrinous pericarditis. The muscle fibers were atrophic and showed marked interstitial edema, and there were numerous small areas of interstitial fibrosis. There was no evidence of Aschoff bodies or Bracht-Waechter lesions.

Examination of the mitral valve and mural endocardium showed that the greater part of the vegetations on the mitral valve consisted of a mass of hyaline thrombus on which was deposited a fresh agglutinated blood platelet thrombus, the surface of which was only partially covered by endothelium. The patches of mural endocarditis showed extensive deposition of hyalinized blood platelet thrombus, the greater part of which was not clothed by endothelium. The endocarditic process had invaded the underlying myocardium rather deeply, with resulting destruction and replacement of many of the muscle fibers (Fig. 2). The deeper layers of both the valvular and the mural lesions were diffusely infiltrated with round cells and showed extensive fibrosis, indicating healing. The patch of mural endocarditis adjacent to the anterior papillary muscles showed infiltration of the thrombotic deposit with calcium salts.

In the lungs, there was organizing fibrinous pleurisy, congestion and edema.

The liver showed parenchymatous degeneration and chronic passive congestion. The central veins were somewhat thickened.

In the spleen, the malpighian bodies were hypoplastic and the pulp showed congestion of the venous sinuses. In the latter were numerous phagocytic cells, containing granules of greenish pigment. At one point, there was a small healed infarct just below the capsule.

In the kidneys, there was universal glomerular injury typical of subacute diffuse glomerulonephritis. The glomeruli showed obliteration of various loops with hyalinization and fibrosis, and adhesions to Bowman's capsule. Many of the glomeruli were completely obliterated. The tubules showed parenchymatous degeneration, and the medium sized arteries presented atherosclerotic thickening. The left kidney showed, in addition, cortical and medullary abscesses.

COMMENT

The outstanding features were the onset with precordial pain followed by glomerulonephritis; the protracted course with irregular fever and progressive anemia; cardiac murmurs; acute pericarditis;

the recurrent crops of white-centered petechiae; arthritis; the symptoms pointing to splenic infarction; nitrogen retention in the blood; anasarca; attacks of abdominal pain and hematemesis simulating Henoch's purpura; localized dermatomyositis; herpes zoster, and repeatedly negative blood cultures. The patient died in uremia. The clinical picture was unique, and it was difficult to arrive at a single diagnosis which satisfactorily explained all the symptoms. The loud widespread systolic murmur which was noted before the development of anemia, the peri-

Fig. 2 (Case 1).—Microscopic section of apical patch of mural endocarditis. There is an extensive superficial deposition of hyalinized thrombotic material, not clothed by endothelium. Advanced fibrosis is present in subendocardial tissues, with destruction and replacement of many of the underlying muscle fibers. There are focal and diffuse areas of round-cell infiltration and vascularization in the deeper layers.

carditis, fever, tachycardia, which was marked even when the pyrexia was low, petechiae and embolic symptoms furnished ample evidence of the existence of some form of endocarditis, and the differential diagosis appeared to lie between subacute bacterial and rheumatic endo-

carditis. The white-centered petechiae, symptoms of splenic infarction and nephritis suggested the former diagnosis; whereas, the pericarditis and marked arthritis pointed toward the latter. On the other hand, white-centered petechiae do not appear in rheumatic endocarditis, and pericarditis is not observed in subacute bacterial endocarditis, except when there is diffuse glomerulonephritis with marked retention of nitrogen.

Because the clinical findings could not be explained by the presence of either form of endocarditis alone, it was concluded that the patient was possibly suffering from a combined infection due to the etiologic agents of both diseases. Had the blood cultures been positive, the diagnosis could have been ventured with greater assurance. Assuming the diagnosis to be correct, it was difficult to account for the occurrence of acute nephritis at the onset of the disease, and the dermatomyositis, the significance of which will be discussed later. Instead of a combined infection of the heart valves, the postmortem examination revealed the peculiar valvular and mural lesions which characterize the atypical form of endocarditis.

CASE 2.—*History.*—E. E.,[2] a woman, aged 37, admitted to the Mount Sinai Hospital, Jan. 25, 1923, gave an unimportant history. Nine months before entering the hospital, she developed painful swelling in both ankles. She had fever and was obliged to remain in bed for a time. Later, the pain spread to various other joints. Three weeks before admission, she suddenly developed chilly sensations, fever, sweats and cough. She was admitted to the hospital, complaining of shortness of breath, painful deglutition and sore throat, symptoms which she had developed during the previous night.

Physical Examination.—The patient was well nourished. She was acutely ill, and had a temperature of 104.8 F. The respiration was labored and rapid, but there was no cyanosis. Over the bridge of the nose, extending symmetrically over both cheeks, was an erythematous eruption of butterfly pattern, resembling acute lupus erythematosus disseminatus. There were also patches of erythema over both elbows. The left third of the upper lip was slightly swollen. On the buccal mucosa of the lower lip was a small area of ulceration, 5 mm. in length, covered by a grayish white membrane. On the dorsal surface of the left side of the tongue near the tip, there was a linear area of ulceration, 1 cm. in length, which was covered by a finely adherent grayish membrane. The margins were dark red, and the surrounding mucosa was infiltrated and purplish. There was marked pyorrhea alveolaris. The pharynx and tonsils were congested, and the vocal cords were swollen and reddened. Below the level of the ninth dorsal spine on the left side, there were flatness and an absence of voice sounds. The breath sounds over this area were scarcely audible. The heart was not enlarged and the action was regular but rapid. The sounds were not altered in quality, and there were no murmurs. The free edge of the liver was felt 4 cm. below the costal margin in the mammillary line. The spleen was not palpable. There was slight swelling of the left elbow joint, but there was no tenderness, and pain was elicited only on extreme extension.

Course.—January 26: The temperature ranged from 102.6 to 103.4 F.; the pulse was 150, and the respiration rate, 40. There were swelling and ecchymosis

2. We are indebted to Dr. N. E. Brill for the privilege of reporting this case.

of both anterior and posterior surfaces of the arytenoids, and edema of the anterior surface of the epiglottis and in both pyriform fossa. The appearance was that of purpuric laryngitis (note of examination by Dr. Yankauer).

January 27: The temperature ranged from 102.8 to 103.2 F.; the pulse was 150, and respiration rate, 34. There were diffuse coarse moist râles, which disappeared after the cough. The left elbow joint was no longer swollen.

January 28: The temperature ranged from 102.2 to 104 F.; the pulse was 130; the respiration rate, 28.

January 29: The temperature ranged from 104 down to 103.4 F.; the pulse was 135; the respiration rate, 26. The signs of fluid at the left base were still present. Over the right lower lobe posteriorly, the breath sounds were suppressed, and there were profuse, inconstant crepitant râles. The lesions on the tongue and lower lip were healing. Several bright red petechiae appeared in the conjunctival mucous membrane of the left lower lid. The fundi showed bilateral neuroretinitis.

January 30: The temperature was 102.4; pulse, 120; respiration rate, 28. Several petechiae appeared in the right lower conjunctiva, one showing a white center.

January 31: The temperature ranged from 102.2 to 104.2 F.; the pulse was 130; the respiration rate, 25. The erythematous lesions on the face were more distinct and darker. Several fresh petechiae were present in the conjunctiva of the upper and lower lids of the right eye. One of these had a white center. The signs in the chest were practically unchanged.

February 1: The temperature range was from 103.4 to 104.2 F.; the pulse was 120; respiration rate, 36. The general condition of the patient had grown worse. Fresh white-centered petechiae were present in the right lower conjunctiva. A pleuro-pericardial friction rub was heard over the fourth left interspace. There were no murmurs at the valve orifices.

February 2: The temperature range was from 104.2 to 107.4 F.; the pulse was 168; respiration rate, 28. The patient was stuporous and somewhat cyanotic. Cheyne-Stokes respiration had set in.

February 3: The neck was rigid, but there were no other signs of meningeal irritation. Over the right lower lobe posteriorly, there was dulness and diminished breathing. The stupor deepened into coma, and the patient died. Shortly before death, the temperature rose to 108 F., the pulse to 190, and the respiration rate to 40.

Laboratory Examinations.—These are presented in Table 2.

Necropsy (eight and one-half hours after death).—The body was that of a well developed and well nourished woman. In the left lower palpebral conjunctival mucous membrane, there was a fading petechial hemorrhage.

The heart was somewhat enlarged. The pericardial investment of the right auricle was roughened, lusterless and covered by a thin layer of fibrinous exudate. There were friable fibrinous adhesions between the parietal pericardium and the left pleura. Numerous small hemorrhages of irregular outline were found beneath the visceral pericardium, especially over the auricles. The tricuspid orifice admitted four finger tips. The tricuspid valve showed patchy fibrous thickening suggestive of a previous attack of endocarditis. Along the line of closure, there was a discontinuous row of granular grayish pink verrucous vegetations, most extensive in the region of the anterior and median cusps, where the lesions were spread over an area of 0.5 cm. in diameter (Fig. 3). There was a fine vegetative deposit on the ventricular aspect of the median cusp, whence there had been extension along the chordae tendineae for a distance of a few millimeters. On the left half of the left posterior cusp of the pulmonary valve, there were several minute slightly raised yellowish gray vegetations, and along the line of attachment of both the right and the left posterior cusps, there was a narrow strip of similar vegetative deposit.

The mitral orifice admitted two fingers. The valve showed diffuse fibrous thickening, most marked in the aortic leaflet. In the region of the junction of the two cusps posteriorly, there was a mass of grayish and grayish pink opaque verrucous vegetations, extending from a point 2 mm. above the closure line as far as the free edge (Fig. 4). There was another group of similar but flatter vegetations along the closure line and free edge where the cusps were joined anteriorly. The endocarditic process, which had also attacked the ventricular aspect of the posterior cusp and the line of attachment of the latter, had spread downward for a short distance along the mural endocardium of the posterior wall of the ventricle. There were several other small patches of mural endocarditis in the left ventricle (Fig. 4). One of these was situated on the papillary endocardium, and several others were in the angle between the tips of the posterior papillary muscle. Similar areas were present in the right ventricle. These patches were irregular in outline and had a diameter varying from 2 to 5 mm. Their surface had an opaque, verrucous appearance, the color

TABLE 2.—*Laboratory Examinations* *

Urine

Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic
1/26	Cloudy	Acid	1.020	+++	0	Hyaline and granular casts
1/28	Clear	Acid	1.025	+++	0	Hyaline and granular casts; a few erythrocytes
2/1	Cloudy	Acid	1.020	+++	0	Hyaline and granular casts

Blood Chemistry

Date	Urea N, Mg. per Hundred C.c.	Uric Acid, Mg. per Hundred C.c.	Creatinin, Mg. per Hundred C.c.
1/27	16.8	2.4	1.0

Blood Counts

Date	Hemoglobin, per Cent.	Red Blood Cells	Color Index	White Blood Cells	Polymorphonuclear Neutrophils, per Cent.	Eosinophils, per Cent.	Lymphocytes, per Cent.	Monocytes, per Cent.	Myeloblasts or Myelocytes	Platelets, per C.c.
1/26	75	.....	....	5,400	68	1	28	3	..	..
1/27	70	3,430,000	0.89	5,000	74	0	24	1	1 (myeloblast)	80,000
1/29	74	3,620,000	1.03	5,200	69.5	0	27.5	1.5	1.5 (myelocytes)	70,000

* January 29: The bleeding time was two minutes; congulation time, seven minutes; capillary resistance test, negative; clot retraction, very slight in twenty-four hours. The Wassermann reaction of the blood was negative. A blood culture was made February 2; the mediums used were bouillon and glucose bouillon flasks, agar and glucose agar plates, and Veillon tubes of glucose agar for anaerobic study; all mediums remained sterile.

being a mottled reddish and yellowish gray. The right auricle was the seat of several patches of mural endocarditis (Fig. 3). Interspersed among the endocarditic lesions was a number of small hemorrhages. The aortic valve was slightly thickened. Crushings of the vegetations were sterile. The myocardium was turbid and brownish, and showed tigering. The coronary arteries and aorta showed a slight degree of sclerosis.

Examination of the lungs revealed, in the left plural cavity, a small effusion. The right lung showed areas of bronchopneumonia in the middle and lower lobes. Both lungs were voluminous and showed edema and congestion.

The liver was enlarged, weighing 2,000 gm. The parenchyma was fatty and showed cloudy swelling and marked chronic passive congestion.

The spleen was enlarged, weighing 600 gm. The malpighian bodies were enlarged and stood out prominently as grayish nodules against a background of dark red congested pulp.

Fig. 3 (Case 2).—Right side of heart. Small flat vegetations are irregularly distributed on tricuspid and pulmonary valves. A narrow strip of endocarditis along the line of attachment of two of the cusps of pulmonary valve may be noted. Patches of mural endocarditis are present in auricle and ventricle.

The kidneys were somewhat swollen and less firm than normally. The capsules stripped with slight difficulty, revealing a smooth mottled surface, studded with irregularly distributed minute hemorrhages. The cortical tissue was somewhat swollen and turbid and a grayish pink, but the striations were distinct, and the glomeruli are not unduly prominent. The medullary pyramids were congested. Numerous minute hemorrhages were present in the mucosa of the pelves. The ureters and bladder were normal.

Microscopic Examination.—In the myocardium, the striations of the muscle fibers were indistinct. There was interstitial edema and slight perivascular fibrosis. Here and there were small areas of interstitial round-cell infiltration. There were no Aschoff bodies.

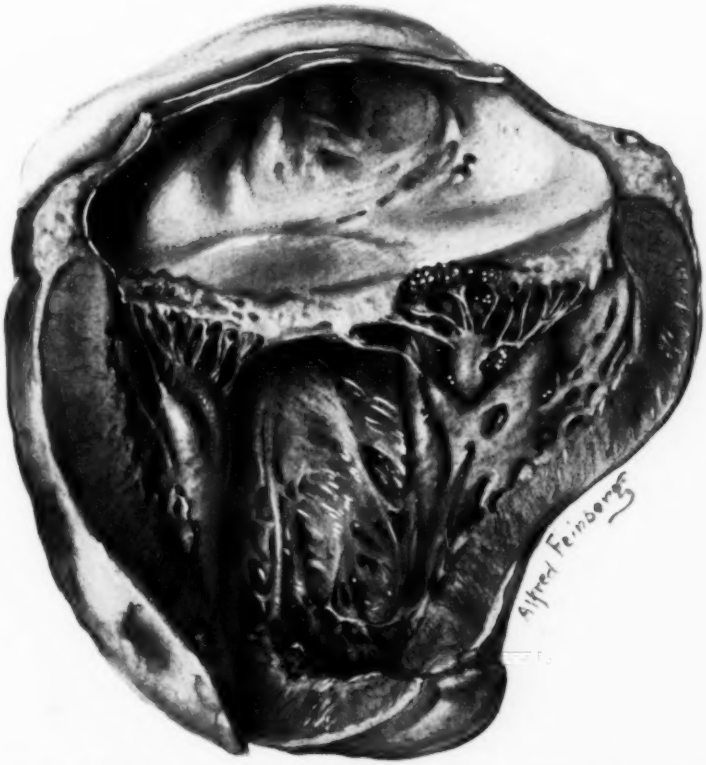

Fig. 4 (Case 2).—Left side of heart. There are verrucous lesions on the mitral valve along the line of closure and the free edge and small islands of mural endocarditis on endocardium of posterior papillary muscle. Extension of the endocarditic process on the mural endocardium of the posterior wall of the ventricle is concealed behind posterior flap of mitral valve.

In the mitral valve were vegetations consisting of a hyalinized thrombus deposited over a fairly extensive area of endocardium. There was but slight cellular infiltration in the subendothelial structures. The vegetations were only in part covered by endothelium. Bacterial stains showed no micro-organisms.

The lungs showed purulent bronchitis and areas of bronchopneumonia. The unaffected alveoli were the seat of marked hemorrhagic extravasation.

The liver showed chronic passive congestion and parenchymatous degeneration. There was marked fatty infiltration of the liver cells in the inner zone of the lobules.

Examination of the spleen showed that the capsule was thickened and there was an organized fibrinous deposit on its surface. The malpighian bodies were large and showed marked diminution of the lymphoid elements. The greater part of each malpighian body was occupied by a number of arterioles, each of which was surrounded by a broad zone of hyaline-like connective tissue. The arteriolar lumen in each instance was diminished in caliber. There were intense congestion of the pulp and dilatation of the venous sinuses.

The kidneys showed congestion, tubular degeneration and medullary edema. There was no glomerulonephritis. The arteries showed atherosclerotic thickening of moderate degree.

COMMENT

The clinical phenomena presented by this patient differed in certain respects from those observed in the previous case. The patient, who had been suffering from polyarthritis for some months, sought medical aid because of the development of a severe respiratory infection, and, in the hospital, the laryngeal symptoms and the presence of pneumonia distracted attention from the heart. The detection of the endocarditis was particularly difficult because of the absence of murmurs and cardiac enlargement. The only finding indicative of infection of the heart valves was the presence of white-centered petechiae in the conjunctival mucous membrane. The friction rub, which proved to be due to pleuropericarditis, might have occurred in the absence of endocarditis. The eruption on the face was of the greatest interest, as a similar eruption was observed in another case of this series. The dermatologists were unwilling to identify these lesions as acute lupus erythematosus disseminatus, but stated that there was a close resemblance. Certain manifestations suggested a tendency to purpura: (1) the hemorrhages into the inflamed laryngeal mucosa, and (2) the low platelet counts and the marked diminution of clot retractibility. Further peculiarities of the underlying infection were the ulcerative lesions of the oral mucosa, the enlarged spleen, the bilateral neuroretinitis and the persistent leukopenia. An attempt to grow organisms from the blood, both aerobically and anaerobically, gave negative results. The postmortem examination, as in the previous case, revealed the lesions of the atypical form of endocarditis.

CASE 3.—*History*.—S. H., a youth, aged 19, admitted to the Mount Sinai Hospital Sept. 16, 1913, with a negative family history, did not remember having any of the acute fevers of childhood. One month before the onset of the present illness, he had an infection of the finger, followed by lymphangitis. Improvement followed incision of the forearm. For six months preceding his admission to the hospital, he had recurrent attacks of pain and swelling in various joints, particularly in the interphalangeal elbow and knee joints. The articular symptoms rarely lasted more than a few days at a time. Five months before admis-

sion, he developed effusion into both knee joints. Two months later, he developed transient hematuria, following the administration of vaccines. The joint symptoms persisted to the time of admission.

Physical Examination.—The patient was well developed and well nourished. The temperature was 101 F. There was no edema, dyspnea or cyanosis. The pupils were equal and regular, reacted to light and contracted during accommodation. The pharynx was negative. Scattered over the skin of the anterior aspect of the chest and the upper arms was a diffuse erythematous eruption, interspersed with small irregular areas of purpura. Scattered over the lower extremities were large red blotches of subcutaneous hemorrhage. The lungs were clear. The heart was not enlarged, and the apex beat was in the left fifth interspace in the mammillary line. The action was rapid and regular, and there were no murmurs. The pulses were equal and the rhythm was regular. The pulse rate was 100. Neither the liver nor the spleen was palpable. There was slight stiffness of both knee joints, the left shoulder joint and all the finger joints. There was no articular swelling. The reflexes were normal.

Course.—September 17: The temperature was 101.2 F.; the pulse, 88; the respiration, 22. The systolic blood pressure was 135.

September 20: The coagulation time of the blood was four minutes.

September 23: The temperature was 98.6 F. The erythematous eruption had disappeared and the purpuric spots were fading. In the last few days, a few small erythematous tender nodules appeared over the elbows and finger tips. Each of these disappeared within twenty-four hours.

September 25: The Pirquet test was negative.

September 30: The temperature was 100.8 F.; pulse, 100; respiration, 24. The cutaneous rash had completely disappeared. The patient developed a painful, tender node over the left wrist yesterday.

October 2: A rough systolic murmur was audible over the pulmonic area.

October 14: The temperature was 100.2 F.; pulse, 98; respiration, 24. The interphalangeal joints of both hands were swollen and almost immobile, but there was no pain or tenderness.

October 26: The temperature was 103.8 F.; pulse, 138; respiration, 24.

November 3: For the last two weeks, the temperature had ranged between 98 and 101.8 F.

November 10: Roentgenographic examination of the chest revealed bilateral pleural effusion and great enlargement of the cardiac shadow.

November 13: The temperature was 101.8 F.; pulse, 116; respiration, 24. For the last three days, the patient had had a feeling of weight over the precordium. The murmur over the pulmonary area was now scarcely audible.

November 14: The temperature was 103 F.; pulse, 128; respiration, 32. A dry leathery pericardial friction rub appeared over the precordium. The patient now complained of definite precordial pain. The apex beat was felt 9.5 cm. to the left of the midsternal line in the fifth interspace. The left border of the heart was found by percussion to be 10 cm. lateral to the sternum in the fifth interspace, and the right border 3.5 cm. to the right in the fourth interspace.

November 15: The temperature was 103.4 F.; pulse, 148; respiration, 46. The precordial pain disappeared, but the patient's general condition was worse. The precordial friction rub was best heard over the left fifth interspace just lateral to the sternum.

November 17: The temperature was 103.2 F.; pulse, 142; respiration, 32. The patient complained of sore throat. The left border of the heart, as determined by percussion, was now 13 cm. to the left of the midsternal line in the fifth interspace and the right border, 7 cm. to the right in the fourth interspace. The physical signs pointed to pericardial effusion. There was flatness at the left base, below the level of the angle of the scapula. Over the right base, there was flatness and diminished breathing, beginning 3 cm. below the level of the angle of the scapula.

November 24: The temperature was 100.2 F. The friction rub had disappeared. There was a short rough systolic murmur over the pulmonary area. No murmurs were heard over any of the other valve orifices.

November 28: The temperature was 102 F.; pulse, 134; respiration, 24. The friction rub was again audible.

December 1: The temperature was 102 F. The signs pointing to bilateral effusion were more marked.

December 3: Five cubic centimeters of sterile, bloody fluid were obtained by aspiration of the left pleural cavity. The cell count was: polymorphonuclears, 15, mononuclears, 85. Roentgenologic examination (Dr. Jaches) revealed no abnormalities in the bones of the hands.

December 9: The temperature was 102 F.; pulse, 148; respirations, 28. The patient vomited several times. The stool showed occult blood. Petechiae were present over the anterior aspect of the chest and abdomen.

December 10: The patient had a generalized convulsion in the morning lasting two minutes, and shortly thereafter died.

Temperature Curve.—September 16-22: The temperature was irregularly remittent, varying from 99 up to 101.4 F., and once reaching 102.6 F.

September 23-October 13: The temperature was usually 98.6 to 99.6; occasionally, 100.6 F.

October 14-25: There were occasional rises to 101.2 F.

October 26: The range was from 103 to 103.8 F.

October 27: The range was from 101.4 to 102.6 F.

October 28-November 3: The temperature ranged from 98 to 101 F.

November 4-10: The temperature was 98.6 to 101.8 F.

November 11-17: There was a gradual irregular rise, in the first few days up to 101.8 F., later to 103.4 F.

November 18-24: The range was from 98.4 to 101.4 F.

November 25-December 4: The temperature was usually 100 to 102 F., at times reaching 103.4 F.

December 5-8: The temperature was not over 100 F.

December 9: The range was from 100 to 102 F.

Laboratory Examinations.—These findings are presented in Table 3.

TABLE 3.—*Laboratory Examinations* *

	Urine †					
Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic
9/17	Clear	Acid	1.030	0	0	Negative
10/30	Clear	Acid	1.024	0	0	Few hyaline casts; numerous leukocytes and epithelial cells
11/22	Clear	Acid	1.020	+	0	A few leukocytes; occasional hyaline casts
12/ 9	Clear	Acid	.....	+	0	Hyaline casts; leukocytes

	Blood Counts							
Date	Hemoglobin, per Cent.	Red Blood Cells	Color Index	White Blood Cells	Polymorphonuclear Neutrophils, per Cent.	Eosinophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.
9/17	..	.....	....	8,600	55	1	32	11
9/22	70	5,000,000	0.7	.....	..	..	..	..
10/27	..	.....	....	10,300	74	0	24	2
11/15	60	3,620,000	0.82	10,200	76	0	16	8

* The Wassermann reaction of the blood was negative. Blood cultures were made October 13 and November 24; both were negative; the mediums used were bouillon and glucose bouillon flasks, and agar and glucose agar plates.

† Amounts varied between 1,100 and 2,300 c.c., usually being less than 1,800 c.c.

Necropsy (Nine hours after death; Dr. Baehr).—The body was that of a well developed, moderately well nourished young man. On the anterior aspect of the chest and abdomen were a few petechiae.

The heart was somewhat enlarged. The lungs were attached to the parietal layer of the pericardium by friable adhesions. Both layers of the pericardium were markedly thickened throughout, and were covered by a thick, shaggy deposit of organizing fibrinous exudate. The parietal layer of the pericardium had been converted into a tough, leathery membrane, measuring from 3 to 4 mm. in thickness. There were multiple friable adhesions between the visceral and parietal pericardium, and within the fibrin meshes there was a good deal of fluid. In the region of the basal portion of the anterior surface of the right ventricle, the adhesions were very dense and quite fibrous. Numerous petechial hemorrhages were scattered over all the pericardial surfaces. The right auricle was dilated. Just above the orifice of the coronary sinus was a slightly raised patch of fibrinous vegetative deposit, measuring 1 by 2 cm. Along its lower border were several petechial hemorrhages. The tricuspid valve admitted four fingers. On all three cusps, there were a number of minute patches of rather flat, yellowish white, opaque, granular deposits situated irregularly along the closure line, extending in places above and below the latter, and also involving the free edge. The infundibular cusp was diffusely thickened, apparently as the result of an old process. Scattered among the endocardial lesions was a number of petechial hemorrhages, the size of a pinhead. The left posterior cusp of the pulmonary valve showed a small patch of a rather flat yellowish white opaque granular deposit, irregular in outline, situated along the line of closure. Spreading downward on the mural end from a point along the line of attachment of this cusp, there was a somewhat elevated area of a yellowish gray opaque verrucous deposit, measuring 0.7 by 0.5 cm. Small flat patches of granular material were present along the line of closure of the anterior and right posterior cusps, and there was a narrow strip of vegetative deposit along the line of attachment of the former cusp.

The left auricle was markedly dilated. The mitral orifice admitted three fingers. Both leaflets of the mitral valve showed marked diffuse thickening, and the edges were rounded. The auricular aspect of the aortic cusp was covered by an extensive plateau-like pinkish gray vegetative deposit, which in places had a granular surface, and in places a verrucous one (Fig. 5). The endocardial lesions extended upward for a distance of 1 cm. above the line of closure, and downward to the free edge, extending for a few millimeters along some of the chordae tendineae. On the ventricular aspect of the aortic cusp, there was a patch of similar vegetative deposit, irregular in outline, measuring 1.0 by 0.7 cm. On the auricular aspect of the posterior cusp, there were similar endocardial lesions which on the medical half extended upward along the wall of the auricle for a distance of 1 cm. The free edge was least involved in the lateral half of this cusp. The vegetative process had extended from the ventricular aspect of the posterior cusp downward on the mural endocardium toward the tip of the posterior papillary muscle. Scattered among the endocardial lesions were numerous small hemorrhages. The aortic valve was negative, except for a narrow strip of verrucous deposit along the line of attachment of the right posterior cusp. There was a number of subendocardial hemorrhages in both ventricles. Crushings of the vegetations from various parts of the heart showed no bacteria in smears or cultures. The myocardium was yellowish brown and cloudy in appearance, and of a rather friable consistency. The coronary arteries and aorta were negative.

In the lungs, both pleural sacs showed a considerable quantity of fluid. There were friable fibrinous adhesions between the visceral and parietal pleura of both upper lobes. Both lower lobes were partly collapsed, and showed intense congestion.

In the esophagus and gastro-intestinal tract, there were numerous petechiae on the mucosa.

The liver weighed 2,050 gm. There was present chronic passive congestion. The wall of the gallbladder was markedly edematous.

November 24: The temperature was 100.2 F. The friction rub had disappeared. There was a short rough systolic murmur over the pulmonary area. No murmurs were heard over any of the other valve orifices.

November 28: The temperature was 102 F.; pulse, 134; respiration, 24. The friction rub was again audible.

December 1: The temperature was 102 F. The signs pointing to bilateral effusion were more marked.

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October 14-25: There were occasional rises to 101.2 F.

October 26: The range was from 103 to 103.8 F.

October 27: The range was from 101.4 to 102.6 F.

October 28-November 3: The temperature ranged from 98 to 101 F.

November 4-10: The temperature was 98.6 to 101.8 F.

November 11-17: There was a gradual irregular rise, in the first few days up to 101.8 F., later to 103.4 F.

November 18-24: The range was from 98.4 to 101.4 F.

November 25-December 4: The temperature was usually 100 to 102 F., at times reaching 103.4 F.

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11/22	Clear	Acid	1.020	+	0	A few leukocytes; occasional hyaline casts
12/ 9	Clear	Acid	.....	+	0	Hyaline casts; leukocytes

	Blood Counts							
Date	Hemoglobin, per Cent.	Red Blood Cells	Color Index	White Blood Cells	Polymorphonuclear Neutrophils, per Cent.	Eosinophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.
9/17	..	.....	....	8,600	55	1	32	11
9/22	70	5,000,000	0.7	.....	..	..	..	..
10/27	..	.....	....	10,300	74	0	24	2
11/15	60	3,680,000	0.82	10,200	76	0	16	8

* The Wassermann reaction of the blood was negative. Blood cultures were made October 13 and November 24; both were negative; the mediums used were bouillon and glucose bouillon flasks, and agar and glucose agar plates.

† Amounts varied between 1,100 and 2,300 c.c., usually being less than 1,800 c.c.

Necropsy (Nine hours after death; Dr. Baehr).—The body was that of a well developed, moderately well nourished young man. On the anterior aspect of the chest and abdomen were a few petechiae.

The heart was somewhat enlarged. The lungs were attached to the parietal layer of the pericardium by friable adhesions. Both layers of the pericardium were markedly thickened throughout, and were covered by a thick, shaggy deposit of organizing fibrinous exudate. The parietal layer of the pericardium had been converted into a tough, leathery membrane, measuring from 3 to 4 mm. in thickness. There were multiple friable adhesions between the visceral and parietal pericardium, and within the fibrin meshes there was a good deal of fluid. In the region of the basal portion of the anterior surface of the right ventricle, the adhesions were very dense and quite fibrous. Numerous petechial hemorrhages were scattered over all the pericardial surfaces. The right auricle was dilated. Just above the orifice of the coronary sinus was a slightly raised patch of fibrinous vegetative deposit, measuring 1 by 2 cm. Along its lower border were several petechial hemorrhages. The tricuspid valve admitted four fingers. On all three cusps, there were a number of minute patches of rather flat, yellowish white, opaque, granular deposits situated irregularly along the closure line, extending in places above and below the latter, and also involving the free edge. The infundibular cusp was diffusely thickened, apparently as the result of an old process. Scattered among the endocardial lesions was a number of petechial hemorrhages, the size of a pinhead. The left posterior cusp of the pulmonary valve showed a small patch of a rather flat yellowish white opaque granular deposit, irregular in outline, situated along the line of closure. Spreading downward on the mural end from a point along the line of attachment of this cusp, there was a somewhat elevated area of a yellowish gray opaque verrucous deposit, measuring 0.7 by 0.5 cm. Small flat patches of granular material were present along the line of closure of the anterior and right posterior cusps, and there was a narrow strip of vegetative deposit along the line of attachment of the former cusp.

The left auricle was markedly dilated. The mitral orifice admitted three fingers. Both leaflets of the mitral valve showed marked diffuse thickening, and the edges were rounded. The auricular aspect of the aortic cusp was covered by an extensive plateau-like pinkish gray vegetative deposit, which in places had a granular surface, and in places a verrucous one (Fig. 5). The endocardial lesions extended upward for a distance of 1 cm. above the line of closure, and downward to the free edge, extending for a few millimeters along some of the chordae tendineae. On the ventricular aspect of the aortic cusp, there was a patch of similar vegetative deposit, irregular in outline, measuring 1.0 by 0.7 cm. On the auricular aspect of the posterior cusp, there were similar endocardial lesions which on the medical half extended upward along the wall of the auricle for a distance of 1 cm. The free edge was least involved in the lateral half of this cusp. The vegetative process had extended from the ventricular aspect of the posterior cusp downward on the mural endocardium toward the tip of the posterior papillary muscle. Scattered among the endocardial lesions were numerous small hemorrhages. The aortic valve was negative, except for a narrow strip of verrucous deposit along the line of attachment of the right posterior cusp. There was a number of subendocardial hemorrhages in both ventricles. Crushings of the vegetations from various parts of the heart showed no bacteria in smears or cultures. The myocardium was yellowish brown and cloudy in appearance, and of a rather friable consistency. The coronary arteries and aorta were negative.

In the lungs, both pleural sacs showed a considerable quantity of fluid. There were friable fibrinous adhesions between the visceral and parietal pleura of both upper lobes. Both lower lobes were partly collapsed, and showed intense congestion.

In the esophagus and gastro-intestinal tract, there were numerous petechiae on the mucosa.

The liver weighed 2,050 gm. There was present chronic passive congestion. The wall of the gallbladder was markedly edematous.

The spleen was somewhat enlarged, weighing 240 gm. Near the lower pole, there was a small infarct 0.3 cm. in diameter, just beneath the surface. There was marked hyperplasia of the malpighian bodies and congestion of the pulp.

The two kidneys weighed 250 gm. There were numerous small hemorrhages in the perirenal connective tissue. The capsules stripped easily, and the surface was smooth and reddish brown in color. The stellate veins were congested. The glomeruli were large and prominent. There was intense congestion of the medulla. The mucosa of the pelvis and ureters showed numerous petechiae.

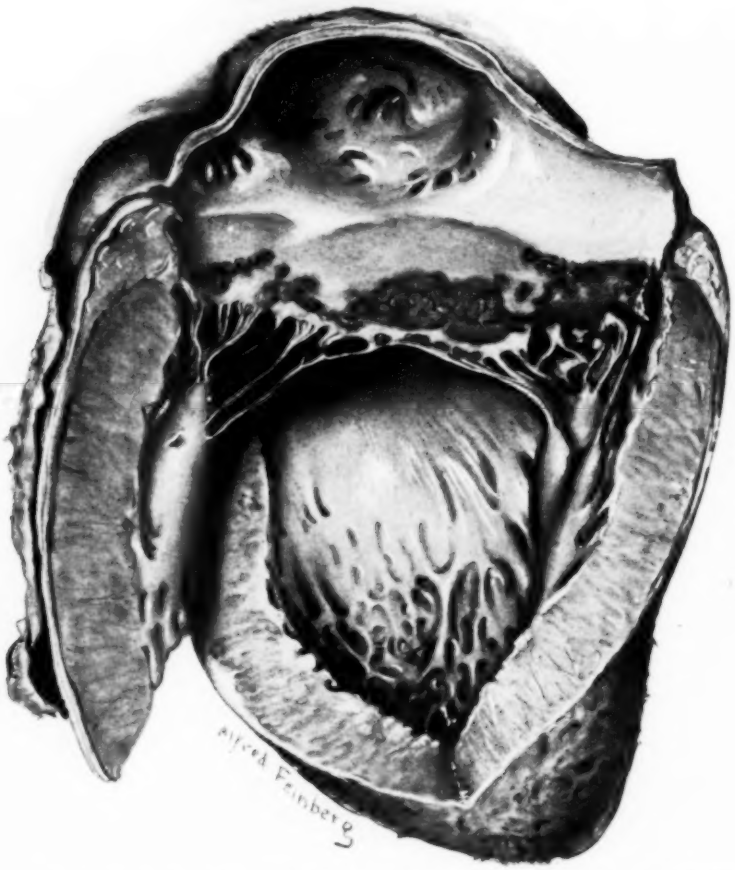

Fig. 5 (Case 3).—Left side of heart. There are extensive flat vegetations on mitral valve and small patches of mural endocarditis on the posterior wall of the ventricle behind the chordae tendineae attached to posterior flap of valve. Universal healing fibrinous pericarditis is present.

Microscopic Examination.—In the mitral valve, there was a deposit of agglutinated blood platelets over large flat areas, beneath which the subendocardial tissues were densely infiltrated with polymorphonuclear leukocytes and round cells, and showed areas of hemorrhage, both recent and old (Fig. 6). The valve itself was enormously thickened owing to an old chronic inflammatory process. Here and there, the dense connective tissue was irregularly infiltrated with round and polymorphonuclear cells. The subendocardial structures were very vascular, and here and there a vessel was almost completely occluded by actively proliferating endothelial cells. The blood platelet masses showed a

Fig. 6 (Case 3).—Ventricular aspect of mitral valve and chorda tendinea. The valve is greatly thickened. There is an extensive superficial deposition of hyalinized blood platelet thrombotic material, partially covered by endothelium, with old scarring and recent fibroblastic invasion and vascularization in subendocardial structures. Focal and diffuse cellular infiltrations, consisting chiefly of polymorphonuclear leukocytes may be noted. There are several small areas of hemorrhage in the deeper layers. On the right is a valvular attachment of greatly thickened chorda tendineae, along which the inflammatory process has spread.

tendency in places to fibroblastic invasion. The inflammatory process extended throughout the entire thickness of the valve, and the vegetative deposit was therefore present on both the auricular and the ventricular aspects of the valve. The vegetative lesions were covered in places by a layer of endothelium.

The chordae tendineae in the neighborhood of their valvular attachments were greatly thickened and showed a deposition of hyalinized thrombus material, and infiltration of the subendothelial structures with polymorphonuclear and round cells. The mural endocardium of the posterior wall of the left ventricle, below the line of attachment of the posterior cusp of the mitral valve, showed extensive deposition of blood platelet thrombotic deposit and infiltration with polymorphonuclear and round cells. The deeper layers showed fibroblastic invasion and fibrous tissue production, and partial destruction and replacement of the underlying muscle fibers. The tips of the posterior papillary muscle and the chordae tendineae near the papillary attachment showed similar changes. No bacteria were present in sections of both the valvular and mitral lesions.

Examination of the pericardium and myocardium showed that the pericardium was greatly thickened. The most superficial layer consisted of masses of fibrin, in the meshes of which were collections of polymorphonuclear cells and a few round cells. Beneath this, there was a layer of loose connective tissue containing numerous fibroblasts and new-formed blood vessels diffusely infiltrated with polymorphonuclear cells. Beneath this layer was a loose connective tissue which was relatively avascular and contained a few cells. Striations of the muscle fibers were somewhat indistinct. There were no Aschoff bodies and no Bracht-Waechter lesions. Special bacterial stains failed to show microorganisms in either the pericardium or the myocardium.

In the liver, there was marked chronic passive congestion, with atrophy of the liver cells in the center of the lobules, and fatty infiltration of the cells in the outer zone. The connective tissue was densely infiltrated in places with round cells.

In the kidneys, the glomeruli showed nuclear increase and a bloodless condition of the capillary loops, resulting from endothelial swelling and proliferation. Many of the glomeruli contained albumin in the capsular space. All the glomeruli were affected, the picture being that of a very early stage of acute diffuse glomerulonephritis. Scattered through the interstitial tissue of both the cortex and medulla were a number of small areas of round-cell infiltration. The medulla showed marked congestion.

In the spleen, the malpighian bodies were marked by hyperplastic. The pulp showed extreme congestion, with dilatation of venous sinuses.

Comment.—The simultaneous occurrence of polyarthritis, endocarditis, pericarditis, and negative blood cultures strongly suggested the diagnosis of rheumatic fever, but certain other findings militated against the latter diagnosis. The record states that the patient developed a number of ephemeral tender erythematous nodes soon after coming under observation. These nodes were apparently identical with the Osler nodes observed in subacute bacterial endocarditis, but they are not seen in rheumatic cases. Moreover, when the patient was first examined, he exhibited a generalized purpuric and erythematous rash of a type we have never observed in a proved case of rheumatic fever. Shortly before death, petechiae and acute glomerulonephritis made their appearance. White-centered petechiae do not occur in rheumatic endocarditis, and petechiae without white centers occur in the latter disease only in association with purpura. Unfortunately, no note was made as to whether or not the petechiae observed in this case had white centers. On the other hand, we have not encountered acute glomerulonephritis in a case of rheumatic fever in which the diagnosis could be

established by the finding of Aschoff bodies in the myocardium. The endocardial lesions found at necropsy were clearly not rheumatic and proved to be of the peculiar type that characterizes the cases constituting the basis of the present communication.

CASE 4.—*History.*—B. M., a girl, aged 10½ years, admitted to the pediatric department of Mount Sinai Hospital, July 24, 1911, had an unimportant family history. She had had measles in infancy, but no other febrile diseases. Ten weeks before admission, she developed pain in both wrists, elbows and shoulders. There were also occasional pains in the joints of the lower extremities. Fever had been present from time to time since the onset. During the week preceding admission to the hospital, the articular pains became less intense, but the patient began to complain of precordial pain, cough, shortness of breath and palpitation. The bowels became constipated and the urine scanty.

Physical Examination.—The patient was well nourished and well developed. The temperature was 101.4 F.; pulse, 136. Her respiration was somewhat accelerated but not labored. On the skin of the bridge of the nose, extending laterally over both cheeks, there was an erythematous eruption of butterfly pattern, which resembled acute lupus erythematosus disseminatus. The skin of the upper part of the anterior aspect of the chest showed patches of erythema. There was brownish pigmentation of the skin over the abdomen. The posterior cervical and axillary lymph nodes on the left side, and the inguinal nodes on both sides were somewhat enlarged. The pharynx was normal. There was slight dulness and suppression of the breath sounds in both lower axillary regions. Posteriorly, there was flatness, extending from a point just above the angle of the scapula to the extreme base on both sides. Here, the breath sounds and the spoken sounds were distant, and there was absence of the whispered voice sounds.

The heart was slightly enlarged, the right border extending 2.5 cm. lateral to the midsternal line in the fourth interspace; the left border being 1 cm. lateral to the mammillary line in the fifth interspace, and the right border 2.5 cm. to the right of the midsternal line in the fourth interspace. The cardiac impulse was seen and felt in the second and third interspace, 2.5 cm. lateral to the mammillary line. The heart action was rapid but regular. A loud, blowing, systolic murmur was audible over the entire precordium. Just within the apex, there was a loud presystolic rumble followed by a snapping first sound. The second pulmonic sound was loudly accentuated. The pulse rate was 136 and the rhythm regular. The abdomen was somewhat distended and tympanitic. The liver was enlarged, extending 7.5 cm. below the costal margin in the mammillary line. The spleen was not felt. There were tenderness and slight limitation of motion of the right wrist joint, the proximal interphalangeal joint of the fifth finger of the left hand, the interphalangeal joints of the right hand and the right knee joint.

Course.—July 26: The temperature was 100.4 F.; pulse, from 136 to 152; respiration rate, 60. Exploratory puncture of both pleural cavities gave negative results. The Pirquet test was positive.

July 30: The temperature was 101 F.; pulse, 130; respiration, 32. A rough pericardial friction rub was audible over the left fourth interspace close to the sternal border.

July 31: The temperature was 104 F.; pulse, 152; respirations, 48.

August 10: The temperature dropped to 100 F., but the pulse was still rapid (130). The pericardial friction rub was ephemeral. There was no precordial pain, dyspnea or cyanosis.

August 16: The temperature was 101.4 F.; pulse, 124. There were slight dyspnea and palpitation, and mild cyanosis of the finger tips. The left border of the heart, as determined by percussion, was 3.5 cm. lateral to the mammillary

line. The friction rub was not heard. A soft, mitral, systolic murmur was heard in the region of the apex. The interphalangeal joints were swollen, but were neither painful nor tender.

August 19: The temperature was 101 F.; pulse, 168; respiration, 68. The joint manifestations had become more marked. There was a peculiar blueness of the fingers, most marked over the swollen proximal interphalangeal joints. The joints of the toes were also swollen, and there was blueness of the skin over both ankles and knees. There was no tenderness, pain or impairment of function of any of the affected joints. A few moist râles were audible over the left upper lobe anteriorly. In the interscapular space, there was an area of dulness, bronchovesicular breath sounds and moist râles. Over the right base anteriorly, there were numerous subcrepitant râles. The pericardial friction rub was again audible. The liver and spleen could not be felt.

August 22: The temperature was 100.4 F.; pulse, 152; respiration, 40. Petechiae appeared for the first time. Several were present in the conjunctival mucous membrane of the right lower lid and in the right bulbar conjunctiva.

August 24: The temperature was 99.8 F.; pulse, 122; respiration, 36. The conjunctival petechiae were fading. A number of petechiae appeared on the back of the shoulders and a few on the abdomen. The cardiac impulse was diffuse and was seen and felt in the second, third and fourth interspaces. The left border of the heart was 9 cm. lateral to the midsternal line in the fourth interspace. The first sound at the apex was followed by a soft systolic murmur. The friction rub was not audible. There was flatness in the left lower axilla and over both lower lobes posteriorly, beginning at the angle of the scapula. Here the tactile fremitus and breath sounds were diminished and a few subcrepitant râles were heard.

August 25: Petechiae had become more profuse over the neck, back and shoulders.

September 7: The temperature was 99 F.; pulse, 112; respiration, 36.

September 11: The temperature was 99.6 F. at 4 p. m. Several hours later, the patient had a sudden attack of dyspnea and cyanosis, with twitchings of the face, left arm and left leg. For a short period, she was unconscious.

September 12: The patient was somewhat stuporous and the temperature rose to 103.4 F. The left leg was paralyzed. The knee jerk was increased on the right side and absent on the left. There was ankle clonus on the right side. The patient vomited several times.

September 13: The temperature was 101.4 F.

September 14: The temperature was 99 F.; pulse, 120; respiration, 32. In the morning, the patient had clonic spasms of the left side, lasting five minutes.

September 15: The temperature rose to 102.6 F., and the pulse rate to 164. The patient vomited several times, and died.

Temperature Curve.—July 24-30: The curve was irregular from 98 to 102 F.

July 31: The range was from 100 to 104 F.

August 1-13: At first, the temperature was from 98 to 99.6 F.; later, 98.6 to 101.6 F.

August 14-20: The temperature ranged from 99 to 102.6 F.

August 21-27: The range was from 98 to 101.6 F.

August 28-September 11: The curve was irregular, from 98.4 to 101 F., and once to 102 F.

September 12: The range was from 101.6 to 103.6 F.

September 13: There was a drop to 98 F.

September 14: The temperature ranged from 99 to 102.6 F.

Laboratory Examinations.—These findings are presented in Table 4.

Necropsy (Nineteen hours after death).—The body was that of an emaciated female child. There were a few petechiae scattered over the anterior aspect of the chest on the right side.

The heart was somewhat enlarged. The pericardial membranes were greatly thickened, and there were fairly dense adhesions between the visceral and parietal layers. The adhesions were edematous, hemorrhagic and friable, and represented fibrinous exudate undergoing organization. The right auricle was dilated. The tricuspid orifice admitted three finger tips. The valve showed slight diffuse thickening, but no definite evidence of a previous attack of endocarditis. Along the line of closure of the anterior cusp and attached to the free edge, there were a few scattered minute granular grayish verrucae in a state of healing. To the right of the tip of the large papillary muscle was a small patch of mural endocarditis, 2 mm. in diameter. The pulmonary valve was negative. The left auricle was moderately dilated. The mitral valve showed diffuse thickening and whitening. Attached to the free edge and ventricular aspect of the posterior cusp, there was an irregular heaped mass of rather firm granular opaque yellowish white vegetative deposit (Fig. 7). The latter was most massive along the ventricular aspect of the posterior cusp, where it reached a thickness of 5 mm. The vegetative process extended to the line of attachment of both cusps, whence it spread downward along the mural endocardium of the ventricle surrounding the upper half of the insertion of

TABLE 4.—*Laboratory Examinations* *

Urine

Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic
7/25	Clear, amber	Acid	1.030	0	0	Negative
8/ 7	Clear, amber	Acid	1.025	Faint trace	0	Negative
8/26	Clear, amber	Neutral	1.012	Heavy trace	0	Red blood cells; a few leukocytes and finely granular casts
8/28	Smoky	Acid	1.022	Heavy trace	0	Many red blood cells, leukocytes, and coarsely granular casts
9/ 4	Smoky	Alkaline	1.018	Heavy trace	0	Numerous red blood cells and white blood cells, and coarsely granular casts

Blood Counts

Date	White Blood Cells	Polymorphonuclear Neutrophils, per Cent.	Eosinophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Monocytes, per Cent.
7/26	6,400	66	4	30	0	0
8/ 1	6,000	71	2	22	4	1
8/15	6,000	72	4	34	0	0
8/19	8,400	78	0	16	6	0
8/31	10,000	84	0	14	2	0

* Blood cultures were taken July 31, August 29 and September 14. There was no growth.

both papillary muscles in crescentic fashion. The papillary endocardium was intact. As the vegetations passed behind the chordae attached to the posterior papillary muscles, they extended forward and downward along the endocardium of the interventricular septum in the form of a lingual process (Fig. 7). The vegetations also extend upward for a short distance along the ventricular aspect of the aortic cusp of the mitral valve. The aortic valve was negative. The vegetation contained no bacteria in smears, crushings and cultures. The left ventricle was hypertrophied, and the myocardium was brownish and cloudy. The coronary artery and aorta were normal.

The lungs showed congestion and areas of bronchopneumonia.

The tracheobronchial and mediastinal lymph nodes were enlarged and firm, and showed gaseous tuberculosis.

The liver was enlarged, weighing 1,500 gm., and showed the typical nutmeg appearance of advanced chronic passive congestion.

The spleen (weight 150 gm.) was enlarged for the size of the child. The capsule was thickened and adherent at numerous points to the diaphragm and

abdominal wall. Beneath the surface were two small wedge-shaped infarcts, the larger the size of a pea. The malpighian bodies were hypoplastic and the pulp showed congestion.

The two kidneys weighed 300 gm. The capsules stripped readily, revealing a smooth surface, grayish brown and studded with numerous small hemorrhages of variable size. There were present marked cloudy swelling and intense congestion. Some of the glomeruli could be made out as tiny red points.

Microscopic Examination.—Myocardium and pericardium showed that the striations of the heart muscle were somewhat indistinct. There were scattered areas of perivascular scarring and round-cell infiltration. Neither Aschoff bodies nor Bracht-Waechter lesions were present. The pericardium

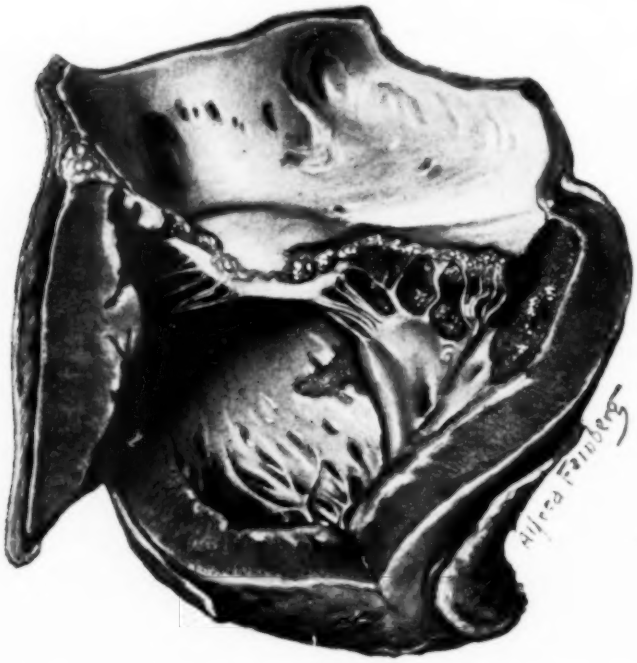

Fig. 7 (Case 4).—Left side of heart. There are vegetations along the line of closure of the arotic cusp of the mitral valve and along the free edge and ventricular aspect of posterior cusp. Extension of the endocarditic process from the line of attachment of the valve downward along the wall of the ventricle and the tips of both papillary muscles, and further spread of the vegetative process on both sides of papillary muscles may be noted. There is a tongue-like projection of vegetative mass on endocardium of interventricular septum.

was markedly thickened, consisting of a layer of edematous tissue infiltrated with round cells and containing numerous dilated blood vessels. Beneath this, there was a layer of vascularized fibrous tissue.

In the mitral valve, the vegetations consisted of a thick layer of thrombotic material attached to the valve by a broad base. The thrombus deposit consisted of pink-staining, partly hyalinized material, representing altered blood platelet

masses, and blue-staining material. Special stains showed no bacteria. In the deeper layer, there was a great deal of vascularized connective tissue containing large numbers of fibroblasts, oval mononuclear cells, round cells and a few polymorphonuclear leukocytes. Phagocytic cells containing yellowish brown pigment were also present.

The lungs showed an advanced grade of chronic passive congestion, with necrosis of the cells in the center of the lobules and marked dilatation of the sinusoids, and fatty infiltration of the cells in the periphery.

Examination of the spleen showed that the malpighian bodies were hyperplastic. Many of the arterioles of the latter showed swelling and proliferation of the endothelium and a variable degree of narrowing of the lumen. Several of the arterioles were plugged with blue-staining thrombotic material, representing small emboli. The pulp showed marked congestion and moderate hyperplasia. The cells lining the venous sinuses were swollen and prominent. Just beneath the capsule was a small healed infarct.

The tracheobronchial lymph node showed an area of caseation, surrounded by a rim of lymphoid tissue containing numerous Langhans' giant cells.

Comment.—The tentative diagnosis at the time of observation was subacute bacterial endocarditis. The main findings were the subacute febrile course, organic mitral lesions, arthritic symptoms, pericarditis, crops of petechiae, eruption on the face resembling acute lupus erythematosus disseminatus, pneumonia and negative blood cultures. The fever, valvular lesion and petechiae strongly suggested the presence of subacute bacterial endocarditis, but doubt would be thrown on the diagnosis if the patient were observed at present, because of the pericarditis, peculiar cutaneous eruption and negative blood cultures. As will be discussed in detail later, a universal fibrinous pericarditis does not occur in subacute bacterial endocarditis as a part of the disease, and, similarly, cutaneous lesions of the character observed in this patient occur in the latter rarely if at all. The failure to grow organisms from the blood does not exclude the presence of subacute bacterial endocarditis.

The bluish discoloration of the painless, swollen joints deserves mention. This finding does not occur in any of the well-recognized forms of endocarditis. The unilateral twitchings and paralysis, and the disturbances of consciousness which occurred several days before death, may have been due to small cerebral emboli, although this cannot be stated with certainty because permission was not granted for an examination of the brain. Embolism does occur in the atypical form of endocarditis as is manifested by the presence of small splenic infarcts in three of the cases.

At the postmortem examination, it was recognized that the endocarditis was of a peculiar type, particularly because of the unusual manner of spread of the endocardial lesions along the posterior wall of the left ventricle. The vegetations were carefully studied for the presence of bacteria, but none were found; yet the histologic examination of the endocardial lesions revealed an active inflammatory process.

It is true that in rheumatic endocarditis one finds active inflammation in vegetations from which bacteria cannot be isolated, but the localization and the gross and microscopic appearance of the endocardial lesions in the case described above were entirely unlike the findings in rheumatic endocarditis. On the other hand, if the lesions were those of active subacute bacterial endocarditis, large numbers of bacteria would have been found in the vegetations.

GENERAL COMMENT

1. *Morbid Anatomy.*—A summary of the pathologic findings observed in our four cases will serve to demonstrate the characteristic lesions of the atypical form of endocarditis and will furnish a basis of comparison for cases observed in the future. In three of the four cases, there was a universal organizing fibrinous pericarditis with friable adhesions between the visceral and parietal layers. In one of these, there was also a sterile pericardial effusion. The pericarditis in the three cases could not be regarded as a terminal infection, as the pericardium showed great thickening, with evidences of advanced organization of the pericarditic exudate. The microscopic examination in one instance revealed marked leukocytic infiltration of a different character from that seen in rheumatic cases. In no instance were micro-organisms found in sections especially stained for their demonstration. In Case 2, there was no exudate on the visceral pericardium, but there was a localized fibrinous deposit on the parietal pericardium, resulting in adhesions to the adjacent pleura.

The distribution of the endocardial lesions is shown in Table 5.

TABLE 5.—*Distribution of Endocardial Lesions*

Tricuspid valve	4
Pulmonary valve	2
Mitral valve	4
Aortic valve	2
Right auricle	2
Left auricle	1
Right ventricle	1
Left ventricle	4

The vegetations on the mitral valve were situated for the most part on the closure line and generally extended both above and below the latter, involving the free edge in places. The lesions in two instances had a definitely verrucous character, in the one being grayish pink and opaque, and in the other more grayish, fibrous and more translucent. The individual verrucae varied in size from 1 to 4 mm., and had in places a rather broad attachment to the valve. In one case, the vegetation had a very extensive attachment to the mitral valve and, though slightly elevated, the lesions had a rather flat surface. In Case 4, the lesions

on the posterior cusp of the mitral valve were situated chiefly on the ventricular aspect of the valve. The mode of extension of the vegetative process from the mitral valve to the mural endocardium was rather characteristic. In each instance, the inflammatory process had spread from the ventricular aspect to the posterior cusp of the mitral valve and the line of attachment of the latter downward along the mural endocardium of the posterior wall of the ventricle for a variable distance. Two of the cases showed small isolated patches of mural endocarditis in the left ventricle, and two in the right ventricle. In one of the former, there was a fairly large area in the region of the apex of the left ventricle (Fig. 1).

All four cases showed lesions on the tricuspid valve, in each instance affecting only a part of the circumference. Here, the lesions were smaller than on the mitral valve; were more irregularly distributed, and were but slightly elevated above the surface. Of special interest was the involvement of the pulmonary valve, as the latter valve is rarely, if ever, involved in rheumatic fever and is very uncommonly affected in subacute bacterial endocarditis.

In Cases 2 and 3, there were small irregular flat lesions on the ventricular aspect of the valve and along the line of attachment of the latter to the ventricle. Two of the cases showed small lesions on the aortic valve. In one of these, there was a narrow strip of endocarditis along the line of attachment of one of the cusps. In two instances, there were flat lesions of irregular outline on the endocardium of the right auricle. Interspersed among the vegetations on the valvular and mural endocardium, there were numerous small hemorrhages. The myocardium showed a variable degree of parenchymatous degeneration, and in one case showed definite fatty changes. The coronary arteries and aorta showed a slight degree of sclerosis.

The microscopic findings were not uniform, but presented certain characteristics in common. The vegetative lesions on the heart valves were capped by blood platelet thrombus deposit showing various degrees of hyaline change. In places, the vegetations were covered with endothelium but large areas remained denuded. In the deeper layers, there were focal and diffuse cellular infiltrations, chiefly of round cells in three of the cases, and predominantly of polymorphonuclear cells in the remaining one. Scattered among the inflammatory foci were numerous small hemorrhages. In places, the entire thickness of the valve was affected by the inflammatory process. The valves in several instances showed diffuse fibrous thickening of the type resulting from previous attacks of endocarditis. In the older lesions, there were areas of fibroblastic invasion, hyalinization of the newly-formed connective tissue and extensive vascularization. In one case, many of the blood vessels in the mitral valve showed marked endothelial proliferation of the

intima. The mural lesions presented a picture similar to that seen on the heart valves. Here, however, the superficial platelet thrombus deposit was more extensive and more massive, and larger areas were denuded of endothelium. The process extended into subjacent structures, destroying and replacing some of the underlying muscle fibers. There were cellular accumulations in the subendothelial tissues and extensive fibrosis in the deeper layers, indicating healing. In the older lesions, both mural and valvular, there was extensive fibroblastic invasion and fibrosis, and a lesser degree of cellular infiltration. The endocarditic lesions in all cases were free of demonstrable bacteria, as determined by studies of smears, cultures and stained sections. The heart muscle showed no Aschoff bodies and Bracht-Waechter lesions. In one case, there was a slight diffuse interstitial fibrosis in the myocardium.

Two of the cases showed bronchopneumonia, and the other two, fibrinous pleurisy with effusion. The liver in three of the cases was enlarged, and showed chronic passive congestion and a variable degree of parenchymatous degeneration. In the remaining case, the liver was small. The spleen in three was enlarged, weighing 240, 150 and 600 gm., respectively. In two of these, the malpighian bodies were enlarged, and in one, the enlargement was due not to hyperplasia of the lymphoid elements, but to a peculiar hyaline thickening around the arterioles. In one of the two cases in which the malpighian bodies were not enlarged, many of the arterioles in the latter showed marked endothelial proliferation of the intima, with marked narrowing of the lumen. In the remaining case, the spleen was small, weighing only 80 gm. Small splenic infarcts were found in three of the cases.

In each instance, the kidneys showed small hemorrhages beneath the capsule, and the parenchyma showed tubular degeneration of variable degree. Diffuse glomerulonephritis was present in two of the cases, acute in one and subacute in the other. In no instance were the embolic glomerular lesions of subacute bacterial endocarditis found.

2. *Clinical Findings.*—Three of the patients were female and one male, the ages being 10½, 19, 24 and 37 years, respectively. None of the patients complained of symptoms referable to the heart prior to the onset of the fatal illness, and none gave a history of chorea. In three of the cases, the disease was ushered in by arthritic symptoms. The initial complaint of the fourth patient was precordial pain, which was followed by arthritis and the manifestations of acute nephritis. The disease in each instance ran a subacute course, lasting from four and a half to nine months. All had pyrexia of irregular type throughout the greater part of the period of observation. One of the patients (Case 1), whose temperature had risen daily to from 101 to 104 F., showed practically no fever during the last month of her life. Another patient

(Case 2), whose temperature during the period of observation was constantly elevated, fluctuating between 102 and 104.6 F., developed hyperprexia shortly before death, the temperature rising to 108 F. In another case (Case 3), the temperature reached from 101 to 102 F. daily, the highest temperature recorded being 103.8 F. In the fourth case (Case 4), the temperature generally rose from 100 to 101.4 F., reaching 104 F. on one occasion. Excessive sweating was not a marked feature and rigors were uncommon. Anemia was noted in each instance and was of moderate severity in all but one case, in which, during the course of six weeks, the hemoglobin percentage fell from 84 to 34, and the erythrocyte count from 5,400,000 to 2,088,000.

The heart showed no great enlargement in any case. Tachycardia was the rule, but at no time was an arrhythmia noted. Murmurs were heard in three cases. In Case 1, the auscultatory signs pointed to mitral insufficiency, and in Case 4, to mitral stenosis and insufficiency. In Case 3, the patient developed under observation a systolic murmur over the pulmonary area. This finding is interesting, in view of the endocardial lesions which were present on the pulmonary valve. In Case 2, no murmurs were heard at any time during the patient's sojourn at the hospital. Three of the patients complained of precordial pain, and in each case a pericardial friction rub was heard. One of these patients developed, in addition, a pericardial effusion. In each instance, the pericarditic manifestations made their appearance at least several weeks before the patient's death. The friction rub heard in Case 2 proved to be pleuropericardial in origin.

Pulmonary symptoms were present in each case. Three of the patients had pleurisy with effusion, and one of these showed in addition outspoken signs of pneumonia. In a fourth patient (Case 4), there were signs of fluid at both bases. She was tapped during life, but no fluid was obtained, and at necropsy no fluid was found; but the method of examination was inadequate to exclude its presence with certainty. Microscopic examination of the lungs revealed areas of bronchopneumonia.

All the patients showed arthritic symptoms, which developed early and recurred from time to time during the course of the illness. The interphalangeal joints, as well as the larger articulations, were affected. The joints were not swollen and red as in typical rheumatic arthritis, and, in two instances, presented certain unusual features. In one case, there were pain and tenderness of the metacarpophalangeal joints of one hand; but, although there was but slight swelling, the overlying skin was of a peculiar red, unlike that seen in typical rheumatic arthritis. In another case, some of the joints were swollen but not tender, and the overlying skin had a bluish color. In the two remaining cases, the joints were painful and tender, and sometimes swollen.

The cutaneous manifestations were of particular interest. All the patients showed petechiae in the skin or conjunctival mucous membrane or both, generally occurring in crops and many having white centers. These petechiae were identical in appearance with those seen in subacute bacterial endocarditis. Two of the patients showed an erythematous eruption of butterfly distribution on the face, which resembled acute lupus erythematosus disseminatus. Both of these patients had erythematous lesions in other parts of the body, and one also showed ulcerative lesions of the buccal and lingual mucosa. A third patient had an eruption involving the entire trunk and extremities, characterized by irregular blotches of purpura interspersed among areas of erythema. In Case 1, a localized bilateral dermatomyositis appeared early in the disease, and later herpes zoster developed.

Because of the friability of the endocardial lesions, embolism can occasionally occur; and, in one instance, the patient experienced symptoms pointing to splenic infarction. Two other cases showed small splenic infarcts at the postmortem examination, but apparently these gave no symptoms during life. One of the patients developed symptoms suggesting cerebral embolism shortly before death, but this could not be confirmed because an examination of the brain could not be made. The finding in one of the cases of tender erythematous nodes which were apparently identical with the Osler nodes seen in subacute bacterial endocarditis is significant because it indicates the possible occurrence of them in the atypical form of endocarditis.

Two of the patients showed acute glomerulonephritis, one at the onset of the disease and the other toward the close. The first of these patients (Case 1) showed albumin, tube casts and erythrocytes in the urine, oliguria, a rise of blood pressure, a marked reduction of the phenolsulphonephthalein output, moderate nitrogen retention, anasarca and convulsions, and finally died in uremic coma. In all probability, the nephritis contributed largely to the severity of the anemia which this patient developed so rapidly. The second patient developed the manifestations of nephritis late in the disease and died in convulsions. The two remaining patients displayed albuminuria and cylindruria, and erythrocytes were present in the urinary sediment; but glomerulonephritis was not found at the postmortem examination.

There seems to be but little tendency to leukocytosis in the instances of the disease thus far observed. In one case, the leukocyte count never rose above 5,600. The highest polymorphonuclear neutrophil percentage noted in this case was 74. In two other cases, the leukocyte counts varied between 6,000 and 10,000, and 8,600 and 10,300, respectively. In Case 1, there was leukopenia early in the disease, later counts rising to 13,400 and 21,600, respectively.

The blood cultures were uniformly negative, despite the employment of methods which gave positive results in more than 90 per cent. of the cases of subacute anhemolytic streptococcus and influenza bacillus endocarditis. Special anaerobic methods were not employed.

Certain of the clinical manifestations, it will be observed, bear a striking resemblance to the symptoms included by Osler in the erythema group. Under the latter designation, Osler included a large number of ill-defined and poorly understood cutaneous visceral manifestations, including certain forms of purpura, angioneurotic edema, erythematous rashes, joint symptoms, ulcerative lesions of the skin and mucous membranes, abdominal colic, pericarditis and acute nephritis. Although these diverse symptoms were grouped under a single designation, a unitary etiology was not hypothecated. It is of interest that in Case 26 of Osler's series, there were lesions in the face which resembled acute lupus erythematosus. It is not improbable that a certain relationship exists between the atypical form of endocarditis and certain of the cases included in the erythema group.

3. Differentiation from Subacute Bacterial and Rheumatic Endocarditis.—In certain respects, the atypical cases resemble both subacute bacterial and rheumatic endocarditis, and yet the differences are quite striking. The differences in the cardiac lesions when comparison is made with rheumatic cases, relate especially to the morphology and distribution of the lesions and to the presence or absence of Aschoff bodies in the myocardium. In typical rheumatic endocarditis, the vegetations consist of small grayish and pinkish gray verrucous structures situated in a row along the line of closure of the valve, rarely involving the free edge or the chordae tendineae. The involvement of the mural endocardium is rare, and when it occurs, is practically negligible. The individual verrucae on the heart valves vary in diameter from 1 to 3 mm., those on a given valve being uniform in size as a rule. Not infrequently, the vegetations are attached to the valve by narrow pedicles. The substance of the vegetations is rather firm. They are crushed with difficulty, and are not easily detached from the valve. Microscopically, the vegetative nodules, in the early stages of their development, consist essentially of a mass of agglutinated blood platelets deposited over a localized area of edematous and actively proliferating subendothelial tissue. The denuded endothelium is quickly replaced by new endothelial cells which grow over the platelet nodule from the adjacent uninvolved valvular endocardium.

In cases of the atypical form of endocarditis, the vegetations frequently have a verrucous character, but tend to be larger and less uniform in size than the typical rheumatic lesions and are attached to the valve by a broader base, which includes the valve above and below the

closure and frequently also the free edge. Unlike those in the rheumatic cases, the lesions involve the line of attachment of the valves and attack the auricular and ventricular endocardium by extension from the valves, and also in isolated patches. The spread of the vegetative process downward along the mural endocardium of the left ventricle and the widely scattered islands of mural endocarditis are in striking contrast to the picture seen in the rheumatic cases. The involvement of the pulmonary valve in two of the cases may be of special significance, as it is of the rarest occurrence in rheumatic fever. It is significant that none of the four cases showed Aschoff bodies in the myocardium. The failure to find these structures is not conclusive proof of the absence of rheumatic infection, as they are not always present in cases that appear to be definitely rheumatic. On the other hand, had Aschoff bodies been found, we should have been obliged to classify our cases as rheumatic, unless a combined infection could have been demonstrated.

Clinically, the differences relate particularly to the cutaneous manifestations and to the occurrence of embolic phenomena. Erythematous lesions on the face resembling acute lupus erythematosus disseminatus such as appeared in the atypical cases do not occur in rheumatic fever. We have never seen petechiae with white centers in a proved case of rheumatic endocarditis. On the other hand, petechiae both with and without white centers were present in each of the four cases described above.

Embolism, when seen in rheumatic cases, generally has its source from a thrombus in the left auricle, occurring in association with mitral stenosis and not from vegetations on the heart valves. The rheumatic verrucae are too firmly attached to the valve to give rise to embolism, and even should an occasional fragment be dislodged, the resulting embolism would be too small to be significant. On the other hand, all sources of embolism, except the valvular and mural endocarditis, could be excluded in explaining the infarction of the spleen that occurred in three of the four atypical cases. As a rule, the spleen is not enlarged in rheumatic fever, but enlargement is seen when the latter disease is associated with status lymphaticus.[3] In three of the four atypical cases, the spleen was enlarged, but in no instance was the organ palpable during life.

Positive statements cannot be made at present concerning the significance of the glomerulonephritis and the purpura which occurred in the atypical group. As far as our experience goes, we have never encountered an instance of acute diffuse glomerulonephritis or generalized purpura in a proved case of rheumatic endocarditis. The atypical and rheumatic forms of endocarditis resemble each other in the occurrence

3. It is surprising how frequently rheumatic fever is associated with status lymphaticus.

of universal fibrinous pericarditis, in the frequent involvement of the tricuspid valve and in the absence of embolic glomerular lesions of the kidneys.

In subacute bacterial endocarditis, the vegetations are larger, more elevated and more friable than in the atypical cases; and, when situated on the mitral valve, characteristically spread upward along the postero-lateral wall of the auricle and downward on the chordae tendineae. Moreover, involvement of the tricuspid and pulmonary valves is exceedingly uncommon (and usually slight) in subacute bacterial endocarditis in the absence of a congenital lesion. A universal fibrinous pericarditis does not occur except in the presence of some complication, or as a terminal event, with uremia. The essential difference between the endocardial lesions of the subacute and atypical cases is that the vegetations in the former contain large numbers of the characteristic organisms, e. g., the anhemolytic streptococci, influenza bacilli and, rarely, gonococci or other bacteria. Moreover, blood cultures are generally positive in cases of subacute bacterial endocarditis.

In both forms of endocarditis, white-centered petechiae are found in the skin and conjunctival mucous membranes. It is not possible to state definitely at present whether a cutaneous eruption resembling acute erythematosus disseminatus can occur in subacute bacterial endocarditis. In a single patient believed to be suffering from the latter disease, a somewhat similar rash was seen. This patient was treated in the open air in a cold atmosphere, and it was not possible to state whether or not exposure to the sunlight and cold played a rôle in the causation of the cutaneous lesions. Unfortunately, a postmortem examination could not be made. Acute diffuse glomerulonephritis with its attendant clinical manifestations occurs in subacute bacterial endocarditis as well as in the atypical cases, but in no instance of the former disease observed thus far have the renal manifestations made their appearance early as in Case 1 of the atypical group.

Embolism occurs in both types of endocarditis, but in the atypical cases it occurs less frequently, and the resulting infarcts are much smaller than in subacute bacterial endocarditis. We have hitherto regarded the ephemeral tender erythmatous nodules (Osler nodes) as pathognomonic of subacute bacterial endocarditis. It is of interest that indistinguishable lesions were recorded as present in one of our cases. On analysis, this finding is not unexpected, as the Osler nodes are due to small arterial emboli. Because of the lesser tendency to embolism in the atypical cases, one should, however, expect to encounter these nodes much less frequently than in subacute bacterial endocarditis.

The so-called Bracht-Waechter lesions, which are so frequently present in the myocardium in cases of subacute bacterial endocarditis, were not found in any of the atypical cases, but as these lesions are not

specific, they have no important differential value. The embolic glomerular lesions described by Loehlein and later studied by Baehr, which are found in almost every case of subacute bacterial endocarditis and have thus far never been found in any other type of endocarditis, were not present in any of our cases.

4. *Etiology.*—We have no clue at present concerning the etiologic agent of the disease. It has already been stated that the blood cultures in each instance were negative, and that there were no demonstrable organisms in the vegetations. Should the anhemolytic streptococcus be isolated from the blood in an occasional case of the disease, it will be necessary to determine whether it is to be regarded as a secondary invader or as indicative of a mixed infection. That the anhemolytic streptococcus is found in the blood in cases of endocarditis in which it is not the causative agent is borne out by the findings of Swift and Kinsella, who were able to grow the organisms from the blood in 8.3 per cent. of a series of cases of rheumatic fever.[4] As we do not know the causative agent, it cannot be stated with certainty that a unitary etiology obtains for all our cases. It must be left to future studies to determine whether the lesions of the atypical form of endocarditis are due to an undescribed virus or are the extraordinary result of the presence of a known etiologic agent.

5. *Diagnosis.*—In view of the limited number of cases of the disease which have been studied, it is obviously unwise to make dogmatic statements concerning the diagnostic value of any one symptom or group of symptoms. The ensuing remarks are based on the assumption that the clinical findings observed in our cases are the typical manifestation of the disease. The simultaneous occurrence of white-centered petechiae and acute pericarditis seems to be the most valuable diagnostic finding. This combination of symptoms occurs:

(*a*) In cases of subacute bacterial endocarditis with advanced renal insufficiency, the pericarditis developing as a terminal uremic manifestation. Acute glomerulonephritis develops occasionally during the active stage of subacute anhemolytic streptococcus (and *Bacillus influenzae*) endocarditis. If death results from uremia while the bacteria are still in the blood, the patient may conceivably develop pericarditis shortly before death. We have never observed such a case, but should one be encountered, the blood cultures would probably be positive and the blood would show marked nitrogen retention. In the healed stage of subacute bacterial endocarditis, advanced renal insufficiency is more common, chronic diffuse glomerulonephritis occurring in about 33 per cent. of the fatal cases that were completely bacteria-free. We have encoun-

4. In contrast to the condition in cases of subacute bacterial endocarditis, no immune reactions to the anhemolytic streptococcus have been found in the cases of rheumatic fever showing bacteremia.

tered one instance of terminal fibrinous pericarditis in a case of this type. The differential diagnosis here presents little difficulty, particularly because white-centered petechiae are not likely to occur in the bacteria-free stage.

(*b*) In cases of combined subacute bacterial and rheumatic endocarditis. The presence of positive blood cultures would furnish the clue to the correct diagnosis. In each of three cases of combined active subacute bacterial and rheumatic endocarditis observed by us, the anhemolytic streptococcus was grown from the blood. It so happened that none of these patients had a recent pericarditis.

(*c*) In cases of acute bacterial endocarditis. The presence of a suppurative focus serving as a portal of entry for the pyogenic bacteria, the acute, stormy course, the Janeway lesions and the positive blood cultures will generally permit the diagnosis to be made with ease. In the staphylococcus cases, the petechiae, in contrast to those seen in subacute bacterial and the atypical forms of endocarditis, often have raised white centers. Moreover, pericarditis is not very common in acute bacterial endocarditis, and, when it develops, is prone to become purulent.

(*d*) In the atypical form of verrucous endocarditis. It will be recalled that three of our four patients displayed white-centered petechiae and acute fibrinous pericarditis, and it appears that the combination of these symptoms in the presence of negative blood cultures will furnish the clue to the diagnosis of many of the cases observed in the future.

The occurrence of an eruption on the face and elsewhere resembling acute lupus erythematous disseminatus is important if only to attract attention to the possible existence of the atypical form of endocarditis. A similar statement applies to generalized purpuric and erythematous rashes of the type included in the erythema group of Osler. We attach great significance to the finding of acute glomerulonephritis in the atypical cases, for we believe that the etiologic agent, or its toxin, has a great affinity for the glomerular endothelium. The occurrence of acute glomerulonephritis has only corroborative value for the diagnosis, however; for it also occurs in subacute bacterial endocarditis. The diagnostic value of this finding would be enhanced if it occurred as an initial symptom, as in Case 1.

In the presence of fever, arthritis, cardiac murmurs, pericarditis, white-centered petechiae, skin rashes of the character described and repeatedly negative blood cultures, the diagnosis should present no difficulties. It seems highly probable, however, that cases will be encountered in which the endocarditic phenomena will be masked by other symptoms. Case 2 is an illustration in point. At no time could murmurs be elicited, in spite of repeated examinations. We have recently observed a patient who appeared to have contracted this disease five

months previously, but as yet no murmurs have appeared. In cases of this kind, a search for white-centered petechiae, unusual cutaneous eruptions, necrotic lesions on the oral mucosa and possibly the skin, embolic phenomena and pericarditis will be required for the detection of endocarditis.

6. *Prognosis.*—The ultimate outcome of these cases is a matter of conjecture. The immediate cause of death in our cases was uremia in two; pneumonia and, apparently, cerebral embolism in another, and pneumonia in the remaining one. It is highly probable that mild instances of the disease will be observed, and from a study of such cases, it may be possible to determine whether this form of endocarditis is capable of producing chronic valvular defects. As subacute bacterial endocarditis is generally engrafted on diseased valves, it will be important to determine how often the latter infection attacks the valves in cases of atypical verrucous endocarditis. It is quite conceivable that such a superadded infection occurs. There is some evidence, both clinical and pathologic, that recurrences develop in the atypical form of endocarditis. In three of the four cases, there were organic changes in the valves indicative of a previous attack of endocarditis. We have recently had under observation a patient who, we believe, developed the disease. He had fever, white-centered petechiae, acute pericarditis, a valvular defect and negative blood cultures. Several weeks after the acute symptoms had subsided and the temperature dropped to normal, he developed a recurrence of the fever, and a fresh crop of white-centered petechiae appeared. He recovered, and now shows only the manifestations of chronic valvular disease.

SUMMARY

We have had the opportunity of studying the clinical and pathologic findings in four cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. In morphology and localization, the endocardial lesions differed from those observed in subacute bacterial, rheumatic and other types of endocarditis. All four valves were involved, and there was a tendency for the inflammatory process to attack the mural endocardium. A uniform finding in our cases was the extension of the endocarditic process from the ventricular aspect of the posterior cusp of the mitral valve along the adjacent mural endocardium of the posterior wall of the ventricle. Isolated areas of mural endocarditis were found in the right auricle and both ventricles. The vegetations were free of demonstrable bacteria and presented a histologic structure which differed in many respects from that of the lesions in other types of endocarditis. The heart muscle showed neither Aschoff bodies nor Bracht-Waechter lesions, and the kidneys showed no embolic glomerular lesions.

The disease, in the form in which it attacked young people who had previously had no organic symptoms, ran a subacute course with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiae, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. One of the patients is said to have had tender erythematous nodules which were apparently identical with the Osler nodes, previously observed only in subacute bacterial endocarditis.

For reasons stated above, the acute pericarditis, white-centered petechiae and negative blood cultures together appears to have diagnostic value, especially in differentiating these cases from rheumatic and subacute bacterial endocarditis. In certain cases, the chief diagnostic problem appears to be the detection of endocarditis; for the manifestations of the latter may be masked by other symptoms. In such cases, the presence of an eruption on the face resembling acute lupus erythmatosus disseminatus or peculiar erythematous and purperic rashes elsewhere should lead to a search for the other manifestations of the atypical form of endocarditis.

Attention was directed to the similarity of certain of the symptoms to those observed in the erythema group of Osler, and to the existence of a possible relationship between certain instances of the latter and the atypical form of endocarditis. The frequency of the disease and the ultimate outcome of nonfatal cases is a matter of conjecture. Future studies must determine whether this form of endocarditis is a potential cause of chronic valvular disease. The etiology is as yet unknown, and it is suggested that, in future studies, the special methods adapted for a cultivation of filtrable viruses and spirochetes be employed among others in the search for the exciting agent.

THE EFFECT OF AMYL NITRITE, BLEEDING AND EPINEPHRIN ON THE BLOOD PRESSURE AND THE SIZE OF THE CAT'S HEART *

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The experiments described in this paper were undertaken with an idea of comparing the relative changes in heart size and blood pressure which occur during vasoconstriction, vasodilatation and bleeding. It is known that the intravenous injection of epinephrin causes a sharp rise in the arterial blood pressure due largely to vasoconstriction.[1] It is known also that the nitrites cause a rapid fall in blood pressure due to a vasodilatation by direct action on the blood vessels.[2] Meek and Eyster,[3] in carefully controlled roentgen-ray studies on dogs found that there was a reduction in the blood pressure and diastolic size of the heart after a hemorrhage amounting to about 2 per cent. of the body weight. Meyer [4] has shown by roentgen ray that hearts of rabbits decrease in size after bleeding. He reported a case of marked diminution in the heart outline following hemorrhage, with a gradual return to normal after recovery of the patient.

Adult cats were used in these experiments. They were etherized, placed on an animal board, and held firmly in position by means of leg ropes and adjustable side arms at the neck and lower border of the thorax. The board was so constructed that the animals rested on a concave surface of lead supported by a wooden frame work. An opening 4 by 5 inches (10 by 12.5 cm.) in diameter in the lead floor directly under the thorax was replaced by a thin aluminum sheet to allow the penetration of the roentgen rays. An 8 by 10 inch (20 by 25 cm.) metal tray supported the screen which moved securely in a 12 by 15 inch (30 by 37.5 cm.) shelf beneath this lead-aluminum floor, directly under the upper abdomen and thorax of the animal. By a manipulation of the tray in four directions, the film was divided into as many quarters, three

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine of the Harvard Medical School.

1. Cushny, A. R.: The Text Book of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1918, p. 367.

2. Sollmann, Torald: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917, p. 376.

3. Meek, W. J., and Eyster, J. A. E.: Am. J. Physiol. **56**:1 (May) 1921.

4. Meyer, E.: Klin. Wchnschr. **1**:1 (Jan. 1) 1922.

of which were at all times cut off from the roentgen rays by means of the lead surfaces, while the fourth rested beneath the aluminum floor. Each quarter was numbered in sequence and designated with the letter of the cat. This method of study permitted a rapid change of films without affecting the position of the animal. A portable roentgen-ray apparatus was used in making the pictures, the tube being held in position 4 feet (1.2 meters) above the animal by means of an upright standard. The exposure was for ten seconds and the current was of 10 milliamperes backed up by a 4½ inch (11.3 cm.) spark gap.

The procedure for study consisted of taking control pictures until a satisfactory position of the chest was obtained. The femoral arteries

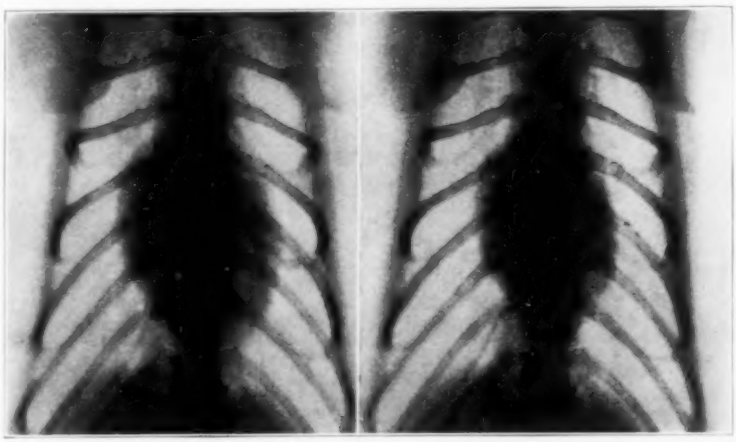

Fig. 1.—Corresponding changes in the heart and blood pressure during vasodilatation and vasoconstriction, and after bleeding. The weight of the silhouettes is expressed in milligrams.

and veins were then exposed, and 100 mg. of heparin [5] dissolved in 2 c.c. of physiologic sodium chlorid solution was injected intravenously. A cannula was inserted in the left femoral artery, it being connected with a manometer apparatus by means of a short rubber tubing. The tubing contained, under slight pressure, 50 c.c. of a 3 per cent. acacia solution and 10 mg. of heparin. Stopcocks, which separated the manometer and cannula from the blood stream of the animal were then released, and a graphic record of the arterial pressure was traced on a smoked drum. At the same time, a roentgenogram was made. This procedure represented the control and is indicated on the graph (Fig. 1) as Period I. Consecutive roentgenograms and pressure tracings were made at dif-

5. Howell, W. H., and Holt, E.: Am. J. Physiol. **47**:328 (Dec.) 1918.

ferent stages during the experiment and are recorded with corresponding numerals on the graph. The changes in heart size were estimated by outlining the heart shadow on the roentgenogram with pencil and tracing a silhouette from this on smooth white paper. The silhouettes were carefully cut and weighed, the weight being accurate to 1 mg. The blood pressure variations were determined by the rise and fall of the pressure curve in relation to the base line.

Since the findings and procedures were practically the same in each cat, one experiment will serve as an example for all. Cat H, a male, weighing 4.2 kg., was etherized and prepared for study as outlined in the plan of technic. After the control picture and blood pressure records were made, an amyl nitrite "pearl" was broken and held in a cone over the animal's nose. Following three or four respirations, the blood pressure fell, and a tracing and a roentgenogram were taken immediately. This procedure represents Period II, and it will be seen on comparing the

Fig. 2 (Cat E, weight 3.2 kg.).—Left: Silhouette of the heart (weight, 558 mg.) before bleeding. Right: Decrease in the heart silhouette of 148 mg. after withdrawal of 28 c.c. of blood.

silhouettes that there was a diminution in heart size with the corresponding fall in blood pressure. Periods III and IV show the return of the pressure to normal with a gradual increase in the heart shadow. Fifteen minutes after the completion of Period IV, 0.25 c.c. of a 1:1000 solution of epinephrin was given intravenously. One minute later, the pressure rose, and a picture was taken as the recording needle reached the highest point on the smoked drum. The heart silhouette in this period (V) was markedly increased in size. The pressure dropped rapidly below normal, and after it had become stabilized another tracing and roentgenogram were made (Period VI). Period VII represents a return of the blood pressure to normal with an enlarged heart area as compared to the preceding period (VI). After the pressure had remained constant for fifteen minutes, 40 c.c. of blood was withdrawn from the left femoral artery. The blood pressure dropped rapidly and was traced at the lowest point. The roentgen-ray silhouette at this time showed a diminution in

heart size. Successive tracings and roentgenograms taken at twenty minute intervals show a gradual although incomplete return to normal. Quite similar results were obtained in other cats.

COMMENT

This experiment suggests the ready adaptability of the heart to changes in the size of the blood vessels. It seems that when the vessels are dilated and the pressure is lowered, the heart diminishes in size. When the vessels are contracted, the blood pressure is elevated and the heart is increased in size. This relationship is expressed in a striking way in Period V when epinephrin was given while the heart was still showing the effects of amyl nitrite by diminished size. Here the outline was greatly increased in all dimensions over any previous silhouette. The very slight increase of heart size in Periods IX and X (after bleeding) as compared to the marked changes following amyl nitrite administration and the secondary effects of epinephrin are due, no doubt, to the loss of fluid from the vessels as the result of venesection. The return to normal is dependent in all probability on the transfusion of fluids from the tissues into the vessel spaces, which occurs slowly. In this regard Meyer [4] has shown that the heart of a rabbit after bleeding does not completely return to normal from twelve to twenty-four hours if the animal is placed in the cage without fluids to drink. He produced, however, a rapid dilatation of the heart after the intravenous injection of colloidal calcium phosphate. We found this to be true in three of the experiments when the heart quickly returned to normal after the injection of a 10 per cent. solution of acacia, equal to the amount of blood withdrawn.

CONCLUSIONS

1. In experiments on cats following the inhalation of amyl nitrite, the heart temporarily decreases in size with a fall in blood pressure.

2. There is a transient increase in heart size with the rise in blood pressure during the vasoconstricting effect of epinephrin.

3. Immediately after bleeding, there is a fall in blood pressure and a corresponding diminution in the size of the heart. The blood pressure approaches normal within a short time, but the heart remains comparatively small.

4. There is a suggested relationship between the blood pressure and changes in the heart size.

RECTAL DIGITALIS THERAPY*

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Not infrequently, patients suffering from heart failure are unable to take digitalis by mouth because of nausea, vomiting or surgical operation. It is in the advanced stages of myocardial insufficiency, at a time when the indications for administering digitalis are most urgent, that nausea and vomiting are often prominent symptoms. The occasional onset of cardiac weakness following operative procedures, when oral medication cannot or should not be resorted to, likewise calls for stimulation of the heart muscle. The margin of safety between therapeutic and toxic dose, when a member of the digitalis group is given by vein, is sufficiently small to render this method of administration hazardous. Concerning the effects of subcutaneous or intramuscular injection, but little definite information is at hand. Such evidence as is available indicates that there is considerable variability in the rate of absorption when digitalis or strophanthin is so given, especially in the presence of circulatory stasis and edema. Furthermore, these substances, being irritants, cause pain when injected into the tissues. The present study was undertaken to ascertain the feasibility of rectal digitalis therapy.

LITERATURE

Only a few fragmentary reports concerning the administration of digitalis by rectum have been recorded. These papers are based largely on clinical impressions. No studies of the rate of absorption have been made.

Eichhorst,[1] in 1916, administered small daily enemas containing digitalis to a group of patients with chronic cardiac insufficiency, and believed that it was in this variety of heart failure rather than in acute decompensation that rectal therapy was indicated. The enema employed, termed by him "mikroclysma," consisted of 5 c.c. of lukewarm water, 10 drops of digalen (Cloetta), 10 drops of tincture of strophanthus and 0.3 gm. theocin. The enema was given each morning over a relatively long period of time. The usual digitalis effects were noted. Interruption in treatment resulted in recrudescence of symptoms. When evidence of irritation of the large bowel appeared, the addition of from 5 to 10 drops of tincture of opium for two or three days served to do away with the discomfort. Vomiting was observed in a few instances and was

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1. Eichhorst, H.: Die Behandlung chronischer Hermuskelinsuffizienz, Deutsch. Arch. f. klin. Med. **118**:337, 1916.

attributed to the theocin. Omission of this drug from the enema, or substitution of another diuretic, abolished this undesirable effect. In patients in whom digitalis, given by mouth, had lost its therapeutic action, Eichhorst believed that the rectal method of administration often proved strikingly effectual.

Morin,[2] following this lead, studied twelve cases in which digitalis was given in the form of suppositories. These contained digalen 1 c.c. (equivalent to 0.15 gm. of digitalis), benzocain and coco butter. He recommended that three suppositories be employed daily for three days, to be followed by two on the fourth day, if necessary. In seven cases, the results were excellent. One patient, though markedly improved after the first course, failed to respond a second time. Four died. All showed characteristic digitalis effects. Morin stated that absorption from the rectum was good, and that the total dosage required for digitalization was identical with the amount required when the drug was given by mouth. In his opinion, the advantage of the rectal method lay in the possibility of administering digitalis to patients who were vomiting. One of the striking results obtained was in a patient with irregular rhythm (probably auricular fibrillation) in whom, prior to medication, the heart rate was 165, the pulse rate, 85. Three days later, after 0.45 gm. digitalis had been given, the heart rate was 80, with all the beats felt at the wrist.

Cloetta,[3] in a discussion of the various methods of administering digitalis, set forth a number of reasons why, *a priori*, absorption from the rectum should be rapid and quantitative. There is no admixture with hydrochloric acid, which this author believes he has shown destroys the activity of the glucosids and forms a combination which is toxic for the nerve centers. In stasis of the mesenteric veins and liver, the absorption of digitalis by mouth may be uncertain. By the administration of the drug by rectum, the portal system is, in a measure avoided, in that all of the blood from the inferior hemorrhoidal veins and part from the middle hemorrhoidals, according to this author, goes directly into the inferior vena cava and thence to the heart. Cloetta also expressed the belief that the prevalent conception, which assumes that the dose of a drug given by rectum must be larger than when given by mouth, is erroneous.

The more recent paper by Meyer [4] adds but little to those just cited. He gave 1 c.c. of liquid digipuratum in 10 c.c. of water, in a small

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2. Morin, J.: De l'emploi de la digalène en suppositoires, Rev. Med. de la Suisse Romande **38**:694, 1918.

3. Cloetta, M.: Ueber die Anwendungsweise der Digitalispräparate, Corr.-Bl. f. schweiz. Aerzte **49**:1193 (Aug. 14) 1919.

4. Meyer, E.: Ueber rectale Digitalistherapie, Klin. Wchnschr. **1**:57 (Jan. 8) 1922.

glycerin enema. Like Eichhorst, Meyer believed that patients refractory to digitalis by mouth often responded satisfactorily to the rectal method of treatment.

MATERIAL AND METHOD OF STUDY

Digitalis was administered by rectum twenty-six times to twenty patients. Cases with fibrillation of the auricles were selected for study, in order that the effect of the drug on the heart rate might be employed as one of the criteria of the rapidity of absorption. One case of ectopic auricular tachycardia is included in the series. The patients all suffered

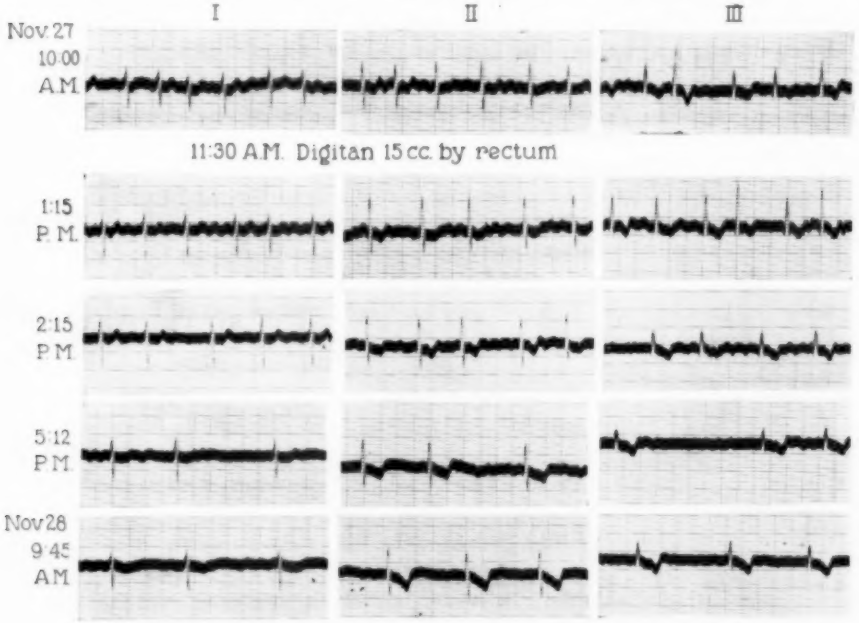

Fig. 1 (Case 1).—Electrocardiograms showing auricular fibrillation. The ventricular rate, November 27, at 10 a. m., was 122; 1:15 p. m., 136; 2:15 p. m., 100; 5:12 p. m., 54; November 28, 9:45 a. m., 60. A change in the form of the T-waves is first apparent in the record made at 1:15 p. m., when T2 and T3 are more deeply inverted. The inversion increases progressively and is most marked, November 28.

from heart failure. In all, the initial ventricular rate was rapid, usually over 120 a minute. The group comprised individuals ranging in age from 9 to 62 years. The clinical conditions associated with auricular fibrillation likewise varied. Depending on the type and extent of myocardial damage, as well as on the presence or absence of edema, serous effusions, infection, etc., variations in the rapidity and degree of digitalis action were to be anticipated.

Some of the patients had received digitalis prior to admission to the hospital; but the amount given was always inadequate to relieve cardiac insufficiency. When the condition of the patient warranted, a preliminary period of several days in bed, without medication, preceded rectal therapy.

After suitable control observations, hourly records of heart and pulse rates were charted for eight hours following the digitalis enema, and at four hour intervals for the next twenty-four hours. In nineteen instances, an electrocardiogram was taken just before administration and approximately every hour thereafter for three, four, or five hours. Another curve was made on the morning following rectal therapy. The electrocardiograms served to check the bedside observations of rate. In addition, they furnished graphic records of alterations in rhythm, when these occurred, and of changes in the form of the T-waves, which are often characteristically altered by administration of digitalis.[5]

PREPARATION EMPLOYED AND TECHNIC OF ADMINISTRATION

The preparation employed was an aqueous solution of purified extract of digitalis leaves called "digitan." One cubic centimeter of the liquid contained the equivalent of 0.1 gm. of powdered leaf. Biologic assay was made by the half hour frog method. The solution was put up in sealed glass ampuls, and was sterilized in them by autoclaving. Tests of biologic activity made after one year showed no deterioration. Clinically, there was no evidence of loss of therapeutic potency after the ampuls had been kept for this length of time.

Early in the course of the work, a tincture of digitalis was used. The alcohol was occasionally found to be irritating to the rectal mucosa unless the dose to be given was diluted to such volume that the enema, because of its bulk, was often expelled. No such difficulties were encountered with the use of the aqueous preparation. The digitalis tincture, properly diluted, may be employed for rectal use.

With one exception, the entire dose of digitalis was given at one time. The patient received a preliminary cleansing enema. After evacuation, from 8 to 20 c.c. of digitan was given by rectal tube and washed through with 25 c.c. of tap water. A rectal tube of small caliber was inserted to a depth of about 6 inches (15 cm.) from the anal orifice. The funnel into which the digitalis was poured was held about 15 inches (37.5 cm.) above the level of the anus. After the tap water had been allowed to flow in, the tube was clamped, left *in situ* for fifteen minutes and then slowly withdrawn. The patients were carefully instructed to resist any desire for a bowel movement for at least six hours.

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5. Cohn, A. E.; Fraser, F. R., and Jamieson, R. A.: Influence of Digitalis on the T-Wave of the Human Electrocardiogram, J. Exper. Med. **21**:593, 1915.

RESULTS

Rate of Absorption.—Retardation in ventricular rate occurred in every instance following digitalis administration (Table 2). As was to be expected, there was commonly coincident diminution in the pulse deficit. The average time necessary for an unmistakable initial effect on rate was two hours and thirty-five minutes.[6] The interval ranged from one hour and fifteen minutes to seven hours and forty minutes. The average time which elapsed before a maximal effect on rate was apparent was nine hours and thirty minutes. This time ranged from

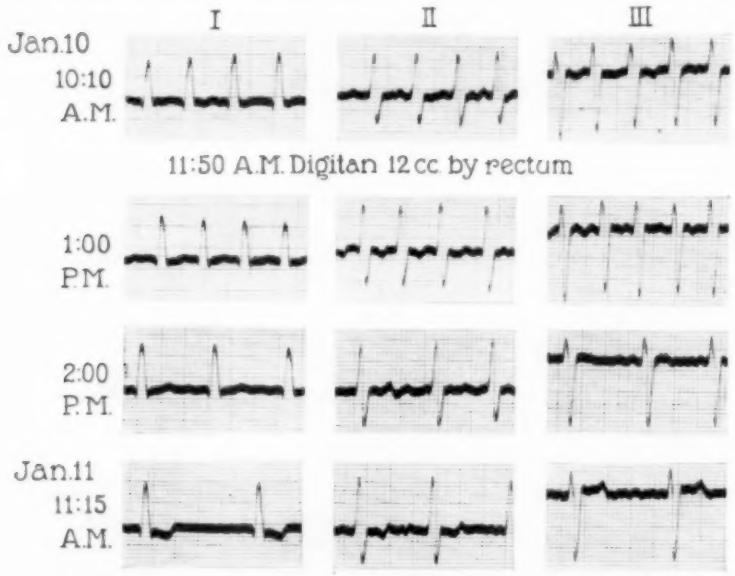

Fig. 2 (Case 2).—Electrocardiograms showing auricular fibrillation. The ventricular rate, January 10, at 10:10 a. m., was 158; 1 p. m., 154; 2 p. m., 80; January 11, 11:15 a. m., 70. A change in the form of the T-waves is first apparent in the record made at 2 p. m., and is more pronounced in the curves taken on the day following rectal therapy.

three hours and fifteen minutes to twenty-two hours (Table 1). It is unnecessary to enter into the clinical details which made inevitable such variations in the time necessary to accomplish the effects observed. Dosage, the degree of decompensation, and the state of the myocardium undoubtedly were cardinal factors which affected the issue. There were probably also individual variations in the rate of absorption.

6. By an unmistakable effect on rate, the beginning of a progressive retardation is meant. This initial fall in rate ranged from 10 to 74 beats, but was, for the most part, from 15 to 30 beats a minute.

A characteristic change in the T-wave of the electrocardiogram occurred in fourteen of the nineteen observations. In five cases, although the rate was slowed, no T-wave change was observed. The initial effect was seen, on an average, in two hours and thirty minutes, approximately the time necessary for a beginning fall in rate. This period varied in length from one hour and twenty minutes to five hours and fifteen minutes (Table 1). Usually, a greater change in the T-wave was seen in the curves made on the morning following digitalis administration (Figs. 1 and 2).

It is of interest to compare the rapidity of digitalis action when the drug is administered in large single doses by mouth, with that observed when it is given by rectum. Robinson,[7] studying the effect of massive oral doses of the tincture (from 15 to 25 c.c.) on the heart rate in cases of auricular fibrillation, observed an initial effect in from two to five hours, a maximal effect in from six to twenty-six hours. Eggleston and

TABLE 1.—*Summary of Twenty-Six Observations on Twenty Patients*

	Time for Initial Effect on Rate	Time for Maximal Effect on Rate	Time for Initial Effect on T-Wave*
Average.....	2 hours, 35 minutes	9 hours, 30 minutes	2 hours, 30 minutes
Range.....	1 hour, 15 minutes to 7 hours, 40 minutes	3 hours, 15 minutes to 22 hours	1 hour, 20 minutes to 5 hours, 15 minutes

* The T-Wave effect was studied in nineteen instances only. In five instances, no change was observed, although an effect on rate was apparent.

Wyckoff [8] found significant differences in the rate of absorption of purified and official tinctures. After the oral administration of large doses of purified tincture, calculated by Eggleston's body weight method, definite evidences of action on the heart were noted in from one to three hours (average, one hour and fifteen minutes). Full therapeutic effects were seen in from four to twenty-four hours (average, fifteen hours and forty-five minutes). The official tinctures were slower in their action. Cohn and Levy,[9] after giving powdered leaves in the form of Merck's digitan, in cases of auricular fibrillation, observed an initial effect on rate in from one to eleven hours (average, three hours and fifteen minutes), and a maximum effect in from one to eighteen hours (average, nine hours). The T-wave of the electrocardiograms, which was altered in 90 per cent. of the cases, showed a beginning change in

7. Robinson, G. C.: Rapidity and Persistence of Action of Digitalis on Hearts Showing Auricular Fibrillation, Am. J. M. Sc. **159**:121 (Jan.) 1920.

8. Eggleston, C., and Wyckoff, J.: Absorption of Digitalis in Man, Arch. Int. Med. **30**:133 (Aug.) 1922.

9. Cohn, A. E., and Levy, R. L.: Unpublished data. A preliminary account of this work appeared in the Proceedings of the Society for Experimental Biology and Medicine **17**:81, 1920.

from seven to forty-eight hours (average, twenty-four hours). It is therefore apparent that the lapse of time necessary for the occurrence of initial and maximal effects on the heart rate in patients with auricular fibrillation, when digitalis is given by mouth, closely approximates that required for the occurrence of similar effects when the drug is given by rectum. The T-wave of the electrocardiogram appears to be affected earlier when the drug is given by rectum.

No observations on the duration of effect were made. The patients chosen for study were, for the most part, seriously ill, and it was con-

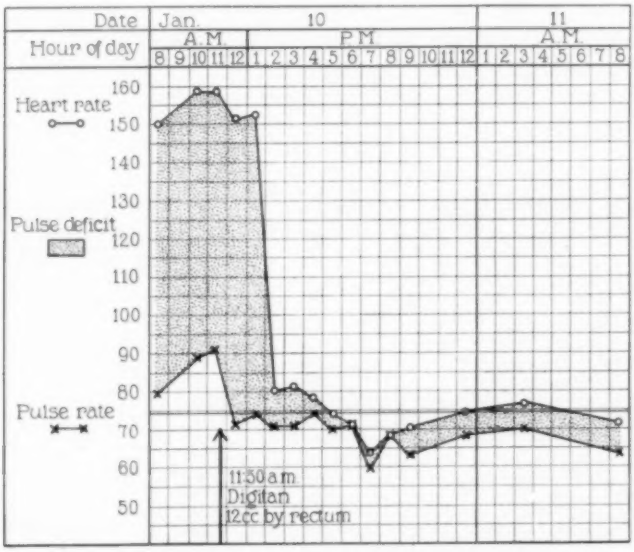

Fig. 3 (Case 2).—Clinical chart.

sidered desirable to continue the administration of digitalis by mouth as soon as this seemed indicated. Furthermore, as will be pointed out, rectal therapy is to be regarded as an emergency measure. The duration of action is therefore not relevant to the problem.

Clinical Effects.—A desirable therapeutic result was apparent in every instance. The usual digitalis effects were observed. In many of the patients, the results were dramatically rapid and beneficial; in others, although there was manifest improvement, further digitalis dosage, by mouth, was necessary to reduce the heart rate to the desired level and to overcome the residual circulatory stasis. In the early stages of the work, relatively small doses of from 8 to 10 c.c. were employed. Later, larger amounts were given. It was found that a safe and effective dose

for a previously undigitalized adult is 15 c.c., containing the equivalent of 1.5 gm. of powdered leaves. This amount is approximately the same as has been found satisfactory in the use of massive doses of digitalis given by mouth.[7] The same considerations which indicate modification of the amount given by mouth serve as indications for varying it when given by rectum. It is of particular importance, in this connection, to take into account any digitalis which may have been given to the patient before rectal therapy is undertaken.

In two patients, in whom absorption was especially rapid and in whom, therefore, a brilliant effect on the circulation was achieved, nausea and vomiting following digitalis administration (Cases 1 and 2, Table 2). The doses in the two cases were, respectively, 12 and 15 c.c. There were no other evidences of untoward digitalis action in any of the patients.

Three patients were vomiting and two suffered from severe nausea at the time of rectal therapy. All were acutely decompensated, and medication by mouth would have been difficult or impossible. The nausea and vomiting promptly disappeared with the subsidence of heart failure.

In two cases, digitalis apparently induced an alteration in rhythm. In one, a woman of 56, with mitral stenosis, who had received no digitalis prior to her admission to the hospital, and in whom the signs of heart failure were not conspicuous, normal rhythm followed the administration of 14 c.c. after the lapse of one hour and forty-five minutes. The duration of the auricular fibrillation was not known; but the patient was at rest in bed in the hospital for twenty-four hours before medication was undertaken. The relationship between therapy and change of rhythm seemed reasonably clear.

The second case was that of a girl of 9 who was critically ill with rheumatic fever, mitral stenosis and insufficiency and pericarditis with effusion. She had had no digitalis, but was intensely nauseated. The heart rate suddenly rose to 166. An electrocardiogram showed an ectopic auricular tachycardia. On the following day, as the tachycardia persisted, 10 c.c. of digitan was given by rectum. After the lapse of thirteen hours and fifty minutes, normal rhythm, with rate of 106, ensued. Three days later, following an exacerbation of the rheumatic infection and an elevation of temperature to 104 F., the auricular tachycardia recurred. In this case, the relationship between digitalis administration and the change in rhythm was probable, but not definitely established.

In order to illustrate more clearly the variety of clinical effects observed, three cases are herewith briefly cited.

REPORT OF CASES

CASE 2.—A man, aged 56, with syphilis, chronic myocarditis, and auricular fibrillation, had been taking quinidin uninterruptedly for a year, with maintenance of sinus rhythm. About two weeks prior to admission to the hospital, he discontinued the drug, and five days later, he was aware of a recurrence of

TABLE 2.—*Clinical Summary of Cases*

Case	Patient	Age	Clinical Diagnosis *	Amt. of Digitalis Given, C.c.	Time for Initial Effect†		Time for Maximal Effect,†	Heart Rate		Remarks
					Rate Hr. Min.	T-Wave Hr. Min.	Rate Hr. Min.	Before Digitalis	At Time of Maximal Effect	
1	J. H.	31	Mitral stenosis and insufficiency	20	1 30	3 15	18 30	125	65	Vomiting before digitalis was given; entire dose not retained
				15	2 45	1 45	5 45	122	54	Vomited after rectal digitalis
2	P. O.	56	Syphilis; chronic myocarditis	12	2 10	2 10	5 10	158	75	Vomited after rectal digitalis
3	A. N.	62	Chronic myocarditis	8	2 5	0 ..	14 15	162	114	Partly expelled 1 hour after administration
				8	7 40	0 ..	19 40	122	88	Died 2 weeks later
4	J. W.	14	Rheumatic fever; mitral stenosis and insufficiency; aortic insufficiency	10	2 10	2 55	4 10	158	110	Partly, though incompletely digitalized; vomiting
				6	1 40	?	11 40	130	86	Second dose given 6 hours after the first
5	J. S.	46	Mitral stenosis and insufficiency; asthma	12	2 45	2 5	6 45	110	76	
6	E. McT.	46	Chronic myocarditis; aortitis	12	4 15	0 ..	4 50	115	80	Enema retained with difficulty; cathartic given that morning
7	S. L.	9	Rheumatic fever; mitral stenosis; pericardial effusion; auricular fibrillation	10	3 50	3 45	15 ..	166	107	Rhythm changed from auricular tachycardia to normal
8	F. K.	51	Mitral stenosis and insufficiency; chronic nephritis	12	1 ..	?	16 ..	110	72	
9	M. McL.	44	Mitral stenosis and insufficiency	12	2 ..	?	6 10	120	90	
				10	3 15	?	6 15	108	96	
10	E. C.	40	Mitral stenosis and insufficiency; aortic insufficiency	12	1 15	1 45	14 15	126	82	Extreme nausea; advanced heart failure
11	S. S.	42	Mitral stenosis and insufficiency	12	2 15	0 ..	11 45	122	78	
12	E. B.	51	Syphilis; myocarditis; hypertension	12	5 ..	5 15	5 ..	96	78	
13	A. P.	39	Mitral stenosis and insufficiency	8	2 15	2 15	7 15	130	72	Vomiting before digitalis was given; none afterward
14	M. C.	56	Chronic myocarditis; hypertension	14	4 45	?	11 45	148	110	Extreme failure
				12	1 30	?	11 30	132	108	Second dose given on day following the first; slow improvement after large doses of digitalis by mouth
15	P. G.	59	Arteriosclerosis; chronic myocarditis; hydrothorax	10	3 15	1 20	3 15	133	104	Extreme failure; prompt diuresis
				12	3 45	1 40	3 45	130	90	Second dose given on day following the first
16	E. G.	59	Mitral stenosis and insufficiency	10	1 30	?	3 25	130	83	
17	M. F.	42	Mitral stenosis and insufficiency	14	1 20	3 30	3 30	110	80	
18	A. W.	48	Mitral stenosis and insufficiency	18	2 5	0 ..	22 ..	128	80	
19	B. E.	56	Mitral stenosis	14	1 45	1 45	.. ..	110	60	Rhythm changed to normal
20	K. H.	52	Chronic myocarditis; hypertension	15	1 50	1 50	6 35	168	76	Paroxysmal fibrillation; regular rhythm returned 4 days later

* In all cases except Case 7 there was auricular fibrillation.
† Time is recorded in hours and minutes.

fibrillation. He attempted to continue at work, but shortness of breath and palpitation forced him to seek medical attention. He took no medicine of any sort before coming to the hospital. On admission, the heart rate was from 150 to 160, with 80 beats coming through to the wrist. After twenty-four hours in bed, during which the heart rate and pulse deficit remained at about the same levels, he was given 12 c.c. of digitan by rectum. Two hours and ten minutes later, the heart rate was 80, the pulse deficit but 8 (Figs. 2 and 3). The maximum effect was apparent seven hours and ten minutes after administration, when the heart rate was 72, with no pulse deficit. Absorption in this case was unusually rapid. The curves shown in Figure 1, taken from another patient, also show a strikingly rapid effect. These two patients were the only ones who suffered from nausea and vomiting after rectal digitalis therapy.

Case 10.—A woman, aged 40, with mitral stenosis and insufficiency, aortic insufficiency and auricular fibrillation, was admitted to the hospital with advanced heart failure. She had taken no digitalis for eight days, but was badly nauseated. The heart rate ranged from 126 to 140, the pulse rate from 116 to 122 a minute. The temperature varied from 101 to 103 F. At 1:45 p. m. on the day following admission to the hospital, 12 c.c. of digitan was given by rectum (Fig. 4). An initial retardation in rate was apparent in one hour and forty-five minutes, and the T-wave first altered its form at about the same time. There was a gradual, progressive fall in heart rate during the next fifteen hours. On the following morning at 8 o'clock, the heart rate was 84, with 78 beats felt at the wrist. The temperature fell to normal coincidently with the subsidence of heart failure, and there was no recurrence of fever.

This case furnishes a striking example of a variety of pyrexia associated with cardiac decompensation, which disappears with reestablishment of an adequate circulation. The slower therapeutic effect in this patient may have been due, in a measure, to the extreme degree of failure which existed at the time digitalis was given.

Case 4.—A boy, aged 14, with subacute rheumatic fever, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, and a greatly hypertrophied heart, had been under observation in the hospital for many months. Although continuously digitalized, there was always some degree of heart failure, which necessitated keeping him in bed. March 13, the oral administration of digitalis was temporarily discontinued. At this time, the heart rate ranged from 76 to 88, with little or no pulse deficit. March 16, the ventricular rate began to rise. During the next ten days, he was given small amounts of digitalis by mouth. He complained of pains in the small joints of the hands.

March 28, the temperature was 101.2 F. The apex rate was 160, the radial rate, 124. The patient was orthopneic and cyanotic, and he complained of precordial pain and cough. There were râles at both lung bases. The liver was 4 cm. below the costal margin. There was no edema. Digitalis, 0.6 gm., was given by mouth.

March 29, the boy appeared to be moribund. He was pale, gasping for breath and irrational at times. The heart rate ranged from 160 to 166. The precordial pain, cough and moist râles at the bases of the lungs were more marked than on the preceding day. He vomited several times after coughing, and was unable to retain medicine by mouth. Intravenous injection of strophanthin semed unwise because of the fairly large amounts of digitalis which had recently been given. At 11:50 a. m., 10 c.c. of digitan was given by rectum (Fig. 5). By 2 p. m. (two hours and ten minutes later), the heart rate had fallen from 160 to 116, with a corresponding fall in pulse rate. At 4 p. m., the ventricular rate was 110, but by 6 o'clock, it had again risen to 130. At this time, however, there was great symptomatic relief. At 6:20 p. m., 6 c.c. of

digitan was given by rectum. There was a gradual retardation of ventricular rate during the night, and by 6 o'clock the following morning, the heart rate was 86, with no pulse deficit. He slept nearly all night. The temperature, which had been 101.8 F. fell to 99 F. From this time on, improvement was continuous. Daily doses of digitalis by mouth were begun. May 18, the boy began to walk. He was discharged from the hospital, July 22.

In this case, rectal digitalis therapy was unquestionably responsible for the saving of life.

Digitalis has been given, by rectum, to twelve patients following surgical operation, in whom signs of cardiac weakness were apparent. Because of vomiting or on account of operations on the upper gastro-intestinal tract, oral medication was impossible. In all, a satisfactory

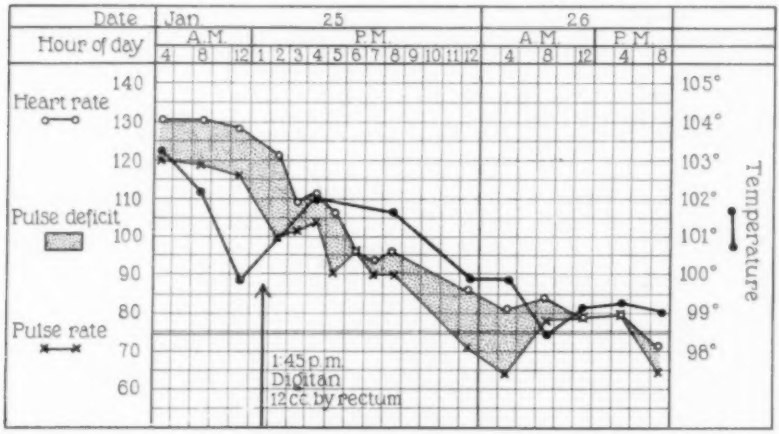

Fig. 4 (Case 10).—Clinical chart.

effect was evident, as measured by ordinary clinical criteria. Accurate graphic control was not employed; nor could the effect on rate be studied, as normal (sinus) rhythm was present in every instance. The studies in the cases of fibrillation, however, permit of the assumption, by analogy, that the drug was absorbed and that whatever beneficial effects were to be anticipated from digitalis under the circumstances, were obtained.

COMMENT

Absorption from the Rectum.—As Cloetta [3] has pointed out, there are *a priori* reasons for believing that the absorption of digitalis from the rectum should be good and its action on the heart relatively rapid. It is profitable, in this connection, to consider briefly the anatomy and venous blood supply of the rectum.

The rectum is from 12.5 to 15 cm. in length. It is sacculated, usually presenting, when distended, three dilatations, of which the lowest and largest, called the *ampulla*, may measure 25 cm. or more, in circumference. This forms a pouch having a relatively large capacity. The rectum has a fairly rich venous blood supply, composed of two plexuses, one internal, lying in the submucosa, another external, resting upon its outer surface. The internal plexus opens partly, at the anal orifice, into the branches of the inferior hemorrhoidal veins, and partly, by branches which traverse the muscular coats, into the external plexus. The latter has three sets of efferent veins: (1) the inferior hemorrhoidals, which empty into the internal pudic, and thence, by way of the internal iliac, into the inferior vena cava; (2) the middle hemorrhoidals, comparatively large veins, which open into the internal iliac or one of its tributaries, and thence into the inferior vena cava, and (3) the superior hemorrhoidals, which empty by way of the inferior mesenteric, into the portal vein.

It is thus apparent that most of the blood from approximately the lower two-thirds of the rectum finds its way directly into the inferior vena cava and to the heart, without going through the portal system and the liver. The introduction of digitalis into the lower rectum may, therefore, reasonably be compared to a slow intravenous injection. It is with this idea in mind that rectal therapy has been advocated in cases of congestive heart failure, when stasis in the splanchnic vessels and swelling of the liver may render absorption from the upper gastrointestinal tract relatively slow.

Two considerations raise the question as to whether this concept is valid from the standpoint of clinical therapeutics. First, the lower two thirds of the rectum is only 3 or 4 inches (7.5 or 10 cm.) in length; and second, the rate of absorption of digitalis when given by rectum, as has already been pointed out, approximates closely that observed when the drug is given by mouth. It was therefore deemed important to determine from what portion of the lower intestinal tract absorption takes place when fluid is introduced into the rectum according to the technic previously outlined. The following simple experiments furnished an answer to this question.

To four convalescent ward patients, 20 c.c. of a 15 per cent. solution of sodium iodid was given by rectal tube and was washed through with 25 c.c. of water, the technic employed being identical with that used in administering digitalis. Fifteen minutes after injection of the iodid, and again approximately two, four and six hours later, roentgenograms of the abdomen were made. The iodid solution, which is similar to that used in pyelography, casts a shadow clearly visible in the roentgenograms.

In three of the patients, some of the solution, immediately after it had been given, was visible in the rectum, but it was for the most part in the lower sigmoid (Fig. 6). In two of these instances, some of the iodid could be seen in the descending colon as high up as the splenic flexure. In the fourth case, all of the iodid was in the sigmoid. In three cases, all of the shadow had entirely disappeared in from four to six hours. In the fourth patient, a considerable amount of the solution was still present in the sigmoid and upper rectum five hours after it had been given. It is thus apparent that, given in the manner described, iodid solution introduced into the rectum remains for the most part in

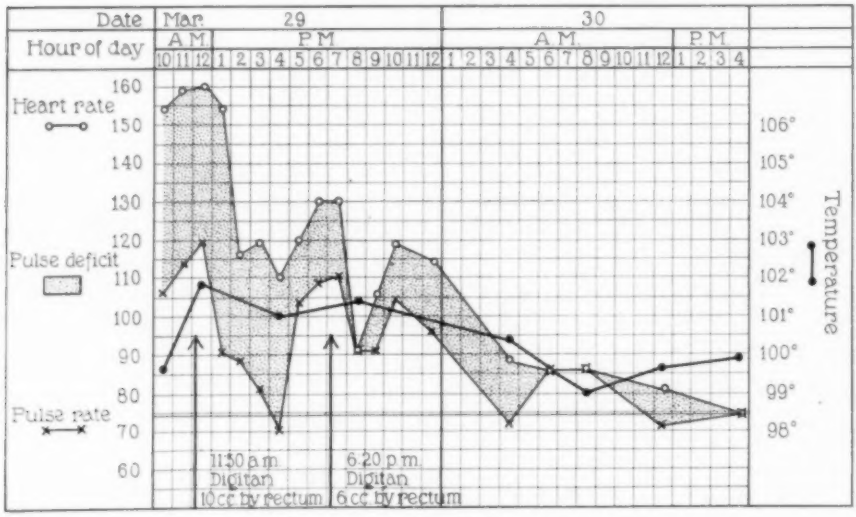

Fig. 5 (Case 4).—Clinical chart.

the sigmoid flexure and is absorbed in from four to six hours. The amount absorbed from the rectum is a small fraction of the amount introduced.

Iodid solution was next given to two other patients in order to determine whether, by employing smaller amounts of fluid and giving more attention to the details of the injection, the liquid could be prevented from going beyond the rectum. A small caliber tube was inserted for a distance of about 2½ inches (6.3 cm.) beyond the sphincter ani and 15 c.c. of iodid solution was washed through with 15 c.c. of water, with the minimum head of pressure necessary to insure flow. Again, although some of the fluid was seen in the rectum, most of it had gone into the distal loops of the sigmoid. As before, absorption was complete in from four to five hours.

These results may be interpreted as indicating that, even with the exercise of reasonable care in introducing such an amount of fluid into the rectum, most of it finds its way at once into the lower loops of the sigmoid and is absorbed from this portion of the intestine. A relatively small amount remains in the upper portion of the rectum and an even smaller quantity is absorbed from that part drained by veins which empty directly into the inferior vena cava. It is clear, then, that digitalis, given by rectum, is taken into the venous circulation for the most part via the mesenteric and portal systems. Hence, it is not surprising to

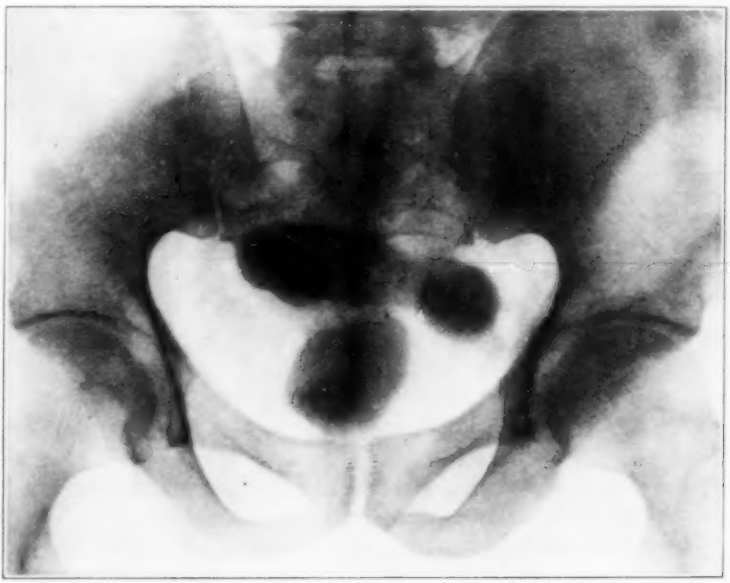

Fig. 6.—Roentgenogram of the lower abdomen twenty-five minutes after administration of 20 c.c. of a 15 per cent. solution of sodium iodid by rectum. The iodid solution was washed through the rectal tube with 25 c.c. of tap water. The entire 45 c.c. was retained and is seen in the rectum and lower sigmoid.

find that the rate of its absorption, as measured by its effects on the heart, is quite comparable to that observed when similar doses are given by mouth

The Place of Rectal Digitalis Therapy in the Treatment of Heart Failure.—When it is possible to give digitalis by mouth, this method of administration is unquestionably the one of choice. Its simplicity, safety and efficacy recommend it. If sufficiently large doses are given, a beginning effect on the heart may be obtained in from two to five hours, a maximal effect in from six to twenty-four hours. Experience justifies

the statement that if a failing heart will respond to digitalis at all, it will react favorably when the drug is given by mouth, provided a potent, absorbable preparation is given in adequate amounts. In those rare emergencies when immediate cardiac stimulation seems imperative, it may be desirable to resort to the intravenous injection of strophanthin.

Rectal digitalis therapy has its field of usefulness, not in supplanting, but in supplementing the oral method of administration. It is to be regarded as an emergency measure, to be used particularly in the presence of nausea or vomiting, or after surgical operation, when oral medication is not feasible. As it has been shown by Hatcher and Weiss [10] that nausea and vomiting, as symptoms of digitalis intoxication, are reflex effects through the direct action of the drug on the heart and are not due to local irritation in the stomach or intestine, similar symptoms may occasionally be anticipated and have, indeed, been observed after rectal administration. The dose of digitalis when given by rectum has been found to be comparable to that employed when a large, single dose is administered by mouth.

SUMMARY

1. Digitalis was administered by rectum twenty-six times to nineteen patients with auricular fibrillation and to one patient with ectopic auricular tachycardia. It has also been given in twelve surgical cases following operation.

2. The preparation employed was an aqueous solution of a purified extract of digitalis leaves. One cubic centimeter contained the equivalent of 0.1 gm. of powdered leaf.

3. The amounts given ranged from 8 to 20 c.c. With one exception, the total dose was administered at one time.

4. The average time necessary for an unmistakable initial effect on rate was two hours and thirty-five minutes. The average time which elapsed before a maximal effect on rate was apparent was nine hours and thirty minutes. A characteristic change in the T-wave of the electrocardiogram occurred in fourteen of nineteen observations. The initial effect was seen, on an average, in two hours and thirty minutes.

5. A desirable therapeutic effect was apparent in every instance. In many of the patients, the results were dramatically rapid and beneficial.

6. Employing a solution of sodium iodid, which casts a shadow in a roentgenogram, it has been shown that fluid introduced into the rectum finds its way, for the most part, into the distal loops of the sigmoid and is absorbed from this portion of the intestine. A small proportion is

10. Hatcher, R. A., and Weiss, S.: Seat of the Emetic Action of the Digitalis Bodies, Arch. Int. Med. **29**:690 (May) 1922.

absorbed from the lower rectum. Most of the digitalis given by rectum reaches the heart via the mesenteric and portal veins and not by way of the inferior vena cava.

7. Rectal digitalis therapy is intended to supplement, not supplant, the oral method of administration. It is useful in the presence of nausea and vomiting, or after surgical operation, when oral medication is not feasible. The dose is comparable to that employed when a large single dose is given by mouth.

DIFFERENTIAL IMPROVEMENTS IN THE SYMPTOMS OF TOXIC GOITER DURING ROENTGEN-RAY TREATMENT AND REST *

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The value of the basal metabolic rate as an index of the degree of toxicity in goiter has been fully discussed by Du Bois,[1] Means,[2] McCasky,[3] Boothby [4] and others. The influence of roentgen-ray treatment on the symptoms of toxic goiter appears to be variable. Halsted [5] (1914) states that selected cases of exophthalmic goiter show improvement after treating the thymus gland with roentgen ray. Seymour [6] (1916) briefly reports the effect of roentgen-ray treatment in eighty cases of exophthalmic goiter. All but seven of these patients showed marked improvement. Seymour concludes that the pulse rate is nearly always reduced at once, and that an increase in the body weight, improvement in nervous symptoms and tremors and a change in the size and condition of the thyroid gland occur almost immediately. Means and Aub [2] (1919) report on a group of fifteen cases of exophthalmic goiter treated with roentgen ray in which the patients received treatments in varying amounts over a period of from two to three years. This group as a whole showed progressive improvement as measured in terms of the basal metabolic rate. The average metabolism of the group before the treatment was 63 per cent. plus. From two to three years after the treatment, it had been reduced to 13 per cent. plus, and all of the patients were leading normal lives. These authors conclude that, in the majority of cases, the results after from two to three years are as good with roentgen ray as with surgery, and that after surgery, the metabolism shows a rapid preliminary fall and a secondary rise followed by a final fall, and that, with roentgen-ray treatment, there is a progressive fall. Also that the rest factor is not so important with the roentgen-ray treatment, and there are practically no fatalities. The

* From the Hull Physiological Laboratory of the University of Chicago.

1. Du Bois, E. F.: Clinical Calorimetry, Arch. Int. Med. **17**:915 (June) 1916.
2. Means, J. H., and Aub, J. C.: Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Dec.) 1919.
3. McCasky, G. W.: Basal Metabolism Determinations in General Internal Diagnosis, J. A. M. A. **74**:927 (April 3) 1920.
4. Boothby, W. M.: Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77**:252 (July 23) 1921.
5. Halsted: Harvey lectures, 1913-1914, p. 224.
6. Seymour, M.: Boston M. & S. **175**:568 (Oct. 19) 1916.

patients treated surgically get along better and the risk of operation is less if they have previously had the thyroid and thymus glands irradiated.

In a later publication (1923), Means and Holmes [7] review the history of the use of roentgen-ray treatment in exophthalmic goiter, and report on fifty-eight new cases treated with roentgen-ray. These authors also discuss the method of treatment and the difficulty in accurately measuring the dosage. Forty-four of the fifty-eight new cases were exophthalmic goiter. Of these patients, sixteen showed little or no improvement, twelve were cured and sixteen showed some improvement. No patient was made worse by the treatment. Fourteen of the new cases were toxic adenomas. All of these patients showed improvement and five were completely cured. In the toxic adenoma cases, the drop in the pulse rate and basal metabolism, and the gain in body weight were more gradual as the result of the roentgen-ray treatment than in the exoph-

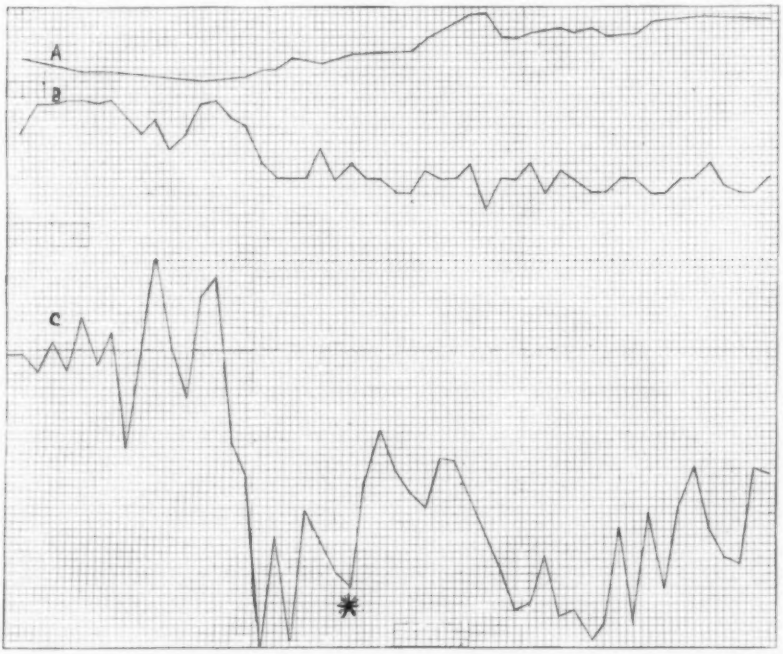

Fig. 1.—Changes in body weight, pulse rate and basal metabolism from June 5, 1921, to D .. 11, 1923. *A*, body weight in kilograms; *B*, pulse rate per minute; *C*, number of calories of heat produced every twenty-four hours. Discontinuation of roentgen-ray treatment is indicated by a star.

7. Means, J. H., and Holmes, G. W.: Roentgen-Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**:303 (March) 1923.

thalmic goiter cases. The authors also state that nine of the cases reported in the 1919 series were still under observation. Six of these patients have normal metabolic rates from five to six years after their first treatment. Another shows an elevation of 6 per cent. Means concludes that the beneficial effects of roentgen rays should be obvious during the first four or five months of treatment and that it seems that the roentgen ray is a useful therapeutic agent in the treatment of toxic goiter.

The case here reported is unique in that the patient's basal metabolism was watched more closely during the period over which roentgen-ray treatments were given than any case previously reported. The basal metabolism of the patient was determined indirectly by means of the Benedict portable respiratory apparatus. The graphic method was used to determine the amount of oxygen consumed. The determinations were

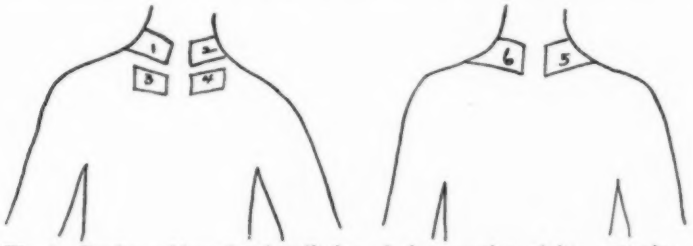

Fig. 2.—Region subjected to irradiation. Left: anterior; right: posterior.

made between 7 and 8 in the morning. A normal individual of the same age, weight, height and sex should have produced 1,665 calories of heat every twenty-four hours.[8] May 21, 1922, the patient ate no food until noon, so that two metabolism determinations were made: one at 7:00 a. m., the other just before noon. The test made just before noon was 7 per cent. higher than the test made at 7:00 a. m.

TABLE 1.—*Roentgen-Ray Treatment of Patient C. C. C.**

Date	Region	MaM	Date	Region	MaM
11/29/21	1-3-5	27	5/12/22	1-2	30
12/ 1/21	2-4-6	27	5/12/22	1-2	30
12/20/21	1-3-5	27	5/ 9/22	1-2	30
12/22/21	2-4-6	27	6/12/22	1-2	30
1/10/22	1	30	6/28/22	1-2	30
	3-5	27	7/14/22	1-2	30
1/12/22	2	30	8/ 1/22	1-2	30
	4-6	27	8/22/22	1-2	30
1/31/22	1	30	10/25/22	1-2	42
	3-5	27	11/ 8/22	1-2	36
2/ 2/22	2	30	11/22/22	1-2	36
	4-6	27	12/ 9/22	1-2	36
2/21/22	1-2	30			

* C. C. C. was the patient of J. L. Miller, M.D. The roentgen-ray treatments were given by H. E. Potter, M.D., to whom I am indebted for the data. In all the roentgen-ray treatments, the filter was 3 mm. of aluminum and 1 thickness of sole leather; the distance, 10″; spark gap, 8.

8. Harris and Benedict: A Biometric Study of Basal Metabolism in Man, Washington, Carnegie Institution of Washington, 1919.

From the tables, it can be seen that the highest metabolism occurred, May 19, 1922. At that time, the rate was 48 per cent. above the normal. Under roentgen-ray treatment and rest, the rate was reduced so that on August 4, it was only 18.6 per cent. above the normal. From Aug. 15, 1922 to June 8, 1923, there was a steady increase in the basal metabolism despite the fact that during this time much roentgen-ray treatment was given, as can be seen from Table 1. The effect of the roentgen ray on the metabolism seemed stimulating rather than depressing. The rate reached a level of 28 per cent. above the normal, but the body weight increased; the pulse rate decreased, and there was a marked improvement in the exophthalmus and other nervous symptoms. From June 8,

TABLE 2.—*Metabolism, Body Weight and Pulse Rate*

Date	Calories of Heat per 24 Hrs.	Pulse	Weight, Kg.	Date	Calories of Heat per 24 Hrs.	Pulse	Weight, Kg.
6/ 5/21	2,325	...	....	3/25/23	2,170	80	69.0
5/ 9/22	2,324	96	68.0	3/26/23	2,139	80	69.0
5/10/22	2,302	104	....	4/ 4/23	2,118	86	71.0
5/11/22	2,340	104	....	4/22/23	2,184	84	72.2
5/12/22	2,307	105	....	5/26/23	2,180	84	73.0
5/14/22	2,376	105	66.4	6/ 8/23	1,969	88	74.0
5/15/22	2,310	104	....	7/19/23	1,920	76	74.2
5/16/22	2,355	105	66.2	9/11/23	2,040	84	71.0
5/17/22	2,199	100	....	9/12/23	1,974	84	70.9
5/18/22	2,293	96	....	9/13/23	1,980	88	71.5
5/19/22	2,462	100	65.8	9/14/23	2,057	80	72.0
5/20/22	2,337	92	....	9/15/23	1,967	86	72.0
5/21/22	2,265	96	....	9/16/23	1,970	84	71.8
5/23/22	2,403	104	65.0	9/17/23	1,935	80	72.2
5/26/22	2,428	105	....	9/18/23	1,953	80	71.2
6/ 6/22	2,206	100	....	9/19/23	2,094	84	71.2
7/24/22	2,159	98	65.6	9/20/23	1,954	84	71.5
8/ 4/22	1,924	88	66.4	11/24/23	2,112	80	73.0
8/ 9/22	1,981	84	66.6	12/ 3/23	2,015	80	73.5
8/11/22	1,933	84	....	12/ 4/23	2,121	84	73.5
8/15/22	2,110	84	67.2	12/ 5/23	2,173	84	73.6
8/23/22	2,078	92	....	12/ 7/23	2,003	88	73.7
8/30/22	2,033	84	67.6	12/ 8/23	2,052	82	73.6
10/22/22	2,012	88	68.7	12/ 9/23	2,046	80	73.6
1/14/23	2,156	84	69.0	12/10/23	2,073	80	73.3
3/ 5/23	2,223	84	....	12/11/23	2,065	84	73.3

to July 19, 1923, there is again a depression, resulting in a basal metabolic rate which averaged only 12 per cent. above the normal. No more tests were made until September 11. At this time, there was a slight increase in basal metabolic rate, with a loss of 5 pounds (2.2 kg.) in body weight. From September 11, to December 11, the metabolism again increased so that it stood 21 per cent. above the normal, but the symptoms of toxic goiter have all practically disappeared.

These improvements may not be due to the roentgen-ray treatments alone, since the patient had been at complete rest for more than nine months before any of the symptoms of toxicity began to subside. Spontaneous remissions equally, or even more, marked have been reported to occur in exophthalmic goiter when the patients were merely on a rest

treatment and that not nearly so complete or prolonged as in this case.[9] The therapeutic value of roentgen-ray treatment in toxic goiter cannot be estimated until more is known in regard to the cause of the symptom complex in this disease. Too much emphasis, no doubt, has been placed on the increased basal metabolism which usually is found in this disease. The basal metabolic rate does not always run parallel with the symptoms of toxicity. In this case, the low metabolism occurred between July 24 and August 11, 1922. After that, excepting for a short period in the summer of 1923 (June 8 to July 19), there has been a constant average increase of 13 per cent. The marked amelioration in the eye symptoms, tremors, tachycardia and body weight has occurred since August 11, 1922, in spite of this increase in metabolism. Repeated irradiation since August 11 has not resulted in a further reduction of the metabolic rate or an ability to maintain it at the lowest level in the course of the treatment.

The most interesting phase of this closely studied case of toxic goiter is the fact that, during the last year, the goiter has been reduced in size; the body weight has increased 15 pounds (6.8 kg.), and the tremors, tachycardia and exophthalmos have been markedly reduced in spite of the fact that the basal metabolic rate has actually increased, so that at the end of the observations it was 21 per cent. plus. The patient is clinically much improved, despite the high basal metabolism. In this case, the symptoms of toxicity do not run parallel with the basal metabolic rate.

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9. Kessel, Leo; Hyman, H. T., and Lande, Herman: A Study of Fifty Consecutive Cases of Exophthalmic Goiter, Arch. Int. Med. **31**:433 (March) 1923.

THE HUMAN THORAX CONSIDERED AS A RESONATOR

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Disturbance of the particles of any elastic body may result in the production of sound waves. The pitch of the sound will depend chiefly on the elasticity of the body and on its mass. When the body consists of a volume of air confined within elastic walls and under the pressure of the atmosphere, its elasticity may be considered to be constant. In this case the pitch of its proper, or fundamental tone is determined by the volume of the contained air if one of the dimensions of the cavity does not greatly exceed the others. In tubes, the diameter remaining unchanged, the pitch of the fundamental tone is determined chiefly by the length of the tube, the longer the tube, the lower the pitch.

The resonator of the physicist is an apparatus used for the analysis of sounds into their component tones. The ideally perfect resonator answers only when a tone of a single definite pitch is sounded before it, the pitch being that of the fundamental tone of the volume of air contained within the resonator. But practically all resonators especially, according to Giesswein,[1] soft-walled resonators, respond to tones other than their fundamental tone. If response is strong to tones nearly of the pitch of their fundamental tone, there is said to be a zone of resonance. When an air space, or other sounding body, vibrates with the production of its proper tone the vibrations are called free vibrations. Vibrations induced in a resonator which are not of the frequency of the fundamental tone are said to be forced on it. Forced vibrations are of much importance in musical instruments. A flat and thin piece of wood, or a stretched membrane, has vibrations of its own proper periodicity, but these are not obtrusive and the structure is so vibratile that it responds readily to tones of widely varying pitch. The sound of a tuning-fork, for example, is reinforced when the fork is set on a flat-topped, wooden table. The reinforcement is greater when the sounding surface overlies an air space. The combination is then called a resonance chamber. The sounding board of the piano with the air within the case is a resonance chamber.

The violin is a still more conspicuous illustration of a resonance chamber, in which tones of a wide range are imparted to the air within the body. The greatest pains are taken by the maker to obtain the most

1. Giesswein: Ueber Brustresonanz, Verhandl. d. Gesell. deutsch. Hals-, Nasen-u. Ohrenärzte, 1921, p. 87.

vibratile wood, and a form of instrument has been evolved empirically which is not only capable of producing strong and rich tones, but also of responding well to tones of widely varying pitch. It is manifestly necessary that the violin shall not act as a resonator, that is, that it shall not especially reinforce the fundamental tone of its cavity. The *f*-shaped slits in the upper surface and the hollows in the sides are said to have for their purpose the prevention of resonator action. The tones of the strings are, then, forced on the violin body, the extraordinarily sensitive wood of which controls the vibrations of the air within, so that the fundamental tone with its free vibrations does not differ noticeably in strength from the forced vibrations of other tones.

But, even in stringed instruments, the volume of the air space cannot be left altogether out of consideration for it governs the range of the vibrations that can be forced on it. So we find that the violin, viola, violoncello and bass viol, while they are all instruments of a wide range of tones, differ in the size of their air volumes, as well as in the length of their strings; high-pitched tones are more easily forced on a relatively small volume of air, very low-pitched tones can only be forced on larger volumes.

Tones may be forced on a resonator in two ways: First, a tone not of its proper frequency may be forced on a resonator to supplant altogether its fundamental tone. An example of this may be found in the reed pipe of the organ. In this kind of a pipe the generator of the resonator action of the pipe is the vibrations of an elastic tongue of metal, called the reed. Such vibrations of a definite frequency and furnished abundant energy by a strong blast of air, influencing, as they do, the air within the pipe to move to-and-fro in a regular way, may succeed in causing the resonator to sound with a tone not of its proper rate of vibration. Practically, this amounts to causing the pipe to be out of tune. The tuner is therefore obliged to tune the reed pipe at the reed as well as at the pipe, whereas, in the case of the flue pipe he needs only to regulate the tone of the pipe.

The second way in which vibrations are forced on a resonator is to cause it to sound to tones not of its proper frequency, in addition to its normal response to its fundamental tone. The resonator has then a zone of resonance. Natural resonators are usually of an improper shape, so that their walls and air volume cannot vibrate fully and entirely even at their normal rate. In cavities, like that of the packing box, in which one diameter exceeds the others to a certain extent as a rule, the long diameter is of importance in determining the pitch of the tone. We may readily see that if the cavity of the resonator is irregular there may be several diameters so nearly of the length of the principal diameter that tones corresponding to them may be heard when mixed vibrations generate sound. This will be particularly true when the generator submits

a noise for resonator action. When a resonator has a zone of resonance under such circumstances, such of the tones of its response as are not of the pitch of its fundamental tone may be said to be forced on it; the important distinction from the first class of forced tones is that the fundamental tone is not affected in pitch by them.

In general, volumes of air confined within elastic walls react most strongly to imparted vibrations by their free vibrations. Vibrations of other periodicities may be forced on a volume of air but only to any considerable extent when they approximate the normal rate of vibration of the cavity, unless the walls are specially constructed to be sensitive to a wide range of sound and the cavity they enclose is shaped accordingly.

A wooden box, covered, or placed bottom up, when struck emits a noise that is a combination of a variety of individual tones. Predominating among the tones of the noise we hear one of relatively low pitch, as compared with the other tones, which is the fundamental tone of the volume of air confined within the box. Given a series of empty wooden boxes of the same general construction, but varying in size, a blind man with a hammer could determine the relative size of each box because the law of response by the fundamental tone is immutable, and the pitch of this tone under the assumed conditions will vary with the size of the box.

The determination of the mode of production of the fundamental tone of the struck wooden box, of the percussed thorax and of the flue pipe of the organ is complicated by the fact that in the cases of the box and of the thorax a concussion is imparted to the contained air, and that in the case of the flue organ pipe a blast of air produces vibrations of the lip of the tube. In these three cases the air volumes do not, properly speaking, function as resonators because the vibrations which excite their proper response simply furnish energy which enables the air to originate its own proper vibrations; in other words, the air is not necessarily excited by communicated vibrations of its own periodicity.

The behavior of the wooden box as a resonator when excited by musical tones may be tested by a simple experiment. Holding a hand saw by the handle in a vertical position, strike the center of the blade with a piece of metal. A sound is produced which is evidently composed of a number of tones of a metallic quality. Lower the saw so that one corner of the lower end of the blade rests on an empty wooden box and exercise sufficient downward pressure so that the blade bends slightly and strike it again. The sound is now of shorter duration, but one of the tones becomes louder and has a "wooden" quality. Repeat this with several boxes and the same result will be obtained, but the pitch of the reinforced tone will vary with the size of the box, boxes smaller than the one first used having higher-pitched, larger boxes lower-pitched

tones. Here a bent sawblade, percussed lightly in a direction perpendicular to its long diameter, can hardly be said to communicate a gross concussion to the box.

When the vibrating saw comes in contact with the box cover the sound waves of the blade, if they do not happen to coincide in periodicity with the free vibrations of the air volume of the box, are forced to a greater or less degree on it. This air volume, being now conjoined with a different vibrating system, is forced to vibrate at a rate which is not that of its normal vibration, the two systems reacting on one another and a tone resulting therefrom which might be called a compromise between the normal vibrations of each, but the pitch of the resonator tone is usually less affected than that of the tone of the generator.

Now, if a single tone had been forced on the boxes, the result would probably be a loud response from one box, less strong responses from larger and smaller boxes of nearly the same size and a feeble response from boxes differing considerably in size. In this case the forcing of tones on the box would be analogous to the forcing of the tones of phonation on the human thorax. For, in the case of the latter a musical tone can only be forced effectively on it when the frequency of the tone is the same, or nearly the same, as that of the fundamental tone of the thorax.

But in the experiment described, instead of a single tone, we have a complex of many tones of varying pitch. The responses of the different boxes, within limits, seems to be about the same, as respects loudness, but the pitch of the predominant tone varies with the size of the box. We must therefore suppose that the individual boxes select different tones for resonation, that, in other words, the reinforcement by each box is that of a tone which lies within the zone of resonance of that particular resonator. We may say therefore that the volume of air of the box governs to a very considerable extent even in the case of well marked musical tones, as it does in the case of communicated concussions. There is an obvious analogy here with the resonation of the thorax which produces the vesicular murmur, as we know it, except that the fact that the vesicular murmur is of the same pitch as that of the percussion note encourages the belief that the larynx, as a generator, does not force the tone on the larynx, but submits vibrations to it which are of its own proper periodicity, so that the response is made by its free vibrations. But in addition to the fundamental tone, since vesicular breathing is a noise, other relatively weak tones which lie within the zone of resonance of the thorax must also be forced on it, so that vesicular breathing furnishes an example of forced vibrations of the second class.

The wooden box so much resembles the thorax, as an acoustic apparatus, that Martini [2] uses the former in his studies of the problems of thoracic sound. The laws set forth with regard to boxes may therefore properly be applied to the thorax. The thorax resonator, however, presents some peculiarities which should be noted. The air cavity of the thorax, like a cushion stuffed with horsehair, is multilocular; solid substances break up the continuity of the volume of the air without, however, preventing it from vibrating as a unit. The normal thorax differs from all other resonators in two respects: First, the solid parts of its contents are largely under a certain definite tension; secondly, it is what might be called a compound resonator. There is the resonator of which the contents, broadly speaking, are represented by the total volume of the air cells, and within this resonator is situated a system of air tubes which is also a resonator but one of a smaller volume, the fundamental tone of which is necessarily of a higher pitch. The proper contents of the larger resonator, having a deep toned fundamental tone, are not adapted to vibrate with the frequency of the air within the bronchial tree. So far, therefore, as vibrations which escape from the bronchi are not of the periodicity of the tone of the larger resonator they are more or less completely damped by the air cells. We may say, then, that in the thorax we have a large resonator in which is contained a small resonator surrounded by insulating material. The insulation varies in thickness and, conformably to that fact, we find that bronchial sounds which are almost entirely excluded in some parts of the lungs, in other parts are forced to a greater or less extent on the air cells and so are transmitted to our ears. The note of percussion is noticeably higher over the upper thorax where bronchial tubes are thinly covered, than it is over the lower thorax where the insulating structures have a greater thickness. In one part of the air tube system, the trachea, there is no insulation and accordingly percussion of this tube gives tympanitic resonance—the fundamental tone of the cavity.

In percussion of the normal thorax the note is composed of quite high tones from the impact of the blow on the pleximeter, moderately high tones from the vibration of the chest wall and also from the resonance of the bronchial system and the deep tones of thoracic resonance. The vibratility of the chest wall may be expected to be practically the same at all points of its surface which are not covered by thick muscles, and its note should therefore be the same. If we find higher pitched tones over the upper thorax than near the base of the lung, we may ascribe the greater prominence of high pitched tones over the upper lung, so far as they do not signify disease, to the normally

2. Martini, Paul: Studien über Perkussion und Auskultation, Deutsch. Arch. f. klin. Med. **139**:65 (April) 1922.

better conduction of sound from the bronchi of the latter region. Practically, in percussion we learn to disregard the pleximeter tones and the tones of the wall, as being constants, and to concentrate our attention on two classes of sound from the lung, the low pitched chest resonance and the group of higher pitched tones.

Martini found the percussion note of the exenterated and inflated lung to be of the same pitch as that of the thoracic note before removal of the lung. The tones of the chest wall are not therefore forced on the lung in such a way as to modify its fundamental tone. This would not be expected if the thorax acts as a resonator, and the fact that they are not is one of the proofs that this is the case. But if the walls of a resonator do not control the vibrations of the air volume they must be controlled by those vibrations. The vibrations of the wall must be the same as the vibrations of the cavity, however they may have originated, and this is as true of the forced vibrations of concussion as it is of the free vibrations that cause the fundamental tone. The drumlike chest wall can conduct very high pitched tones, but so far as it serves as the container of an air volume it is dominated by that volume. It can be shown by a simple experiment that high pitched tones are not forced on the lung. Press a finger firmly against the ear over the auditory meatus, and percuss the part of the finger that lies directly over the meatus with a finger of the other hand. The impact of skin against skin produces loud and high pitched sounds. These disappear if the finger is in the least removed from actual contact with the ear, thus showing that these very high tones have not sufficient energy to survive, as sound, the transition to the air. When the finger is pressed against the chest wall in percussion these tones are lost in the louder and deeper tones, but they are nevertheless still present, for Selling[3] found that resonators answered to the high tones of the pleximeter in finger on finger percussion. But though the solid acoustic media of the chest wall are capable of carrying them around the chest, they are not to be heard posteriorly when percussion is made anteriorly, therefore the vibrations of these sounds not only originate locally in the disturbance of the equilibrium of the skin particles immediately involved, but remain localized in the sense that the lung does not vibrate in response as a resonator. Such vibrations as may be communicated to the lung, if they are reinforced by it, receive only a local reinforcement from air cells directly implicated in the concussion, not a reinforcement of the air cells acting as the content of a resonator, and the lung does not allow the chest wall to vibrate in response to them, as the wall of a resonator.

This interpretation is substantiated by the phenomena of coin percussion. The familiar coin test in pneumothorax is based on the prin-

3. Selling: Deutsch. Arch. f. klin. Med. **90**:163, 1907.

ciple that normal lung tissue prevents the chest wall from transmitting vibrations which the latter is able to transmit when not in contact with lung tissue. As is well known, if a silver coin is laid on the chest and percussed with another coin of the same metal, in pneumothorax the "silvery" sound is carried through the chest and may be heard distinctly over the back when percussion is made anteriorly. This test is distinctive of pneumothorax for the reason that it disappears in the case of the normal lung. The lower tones of the sound are indeed audible, but the very high pitched silvery sound is not. Now, the success of the experiment in pneumothorax shows that the failure to transmit the silvery sound in health is not to be ascribed to the chest wall. It might be supposed that since, as shown in pneumothorax, the chest wall can transmit the silvery sound, this sound would be carried around the chest without passing through the normal lung and should be heard by the observer who listens behind, which we know is not the case. The explanation is furnished by the observations of Jacobson and Danielopolu,[4] who found that when percussion is made over the absolute heart dulness, or the liver, and the second observer auscultates behind just below the level of the normal lung the silvery sound is to be heard. Here the conduction is effected through airless organs, the heart and liver. The observation shows that the thoracic wall is abundantly able to transmit the silvery sound in health, so far as its own vibrations are concerned, but there wherever it is in contact with the lung it acts as the wall of a resonator and cannot therefore vibrate to high pitched tones to which its contents are deaf. At the same time, the lung tissue which is sometimes spoken of as sluggish conducts lower pitched tones so well that the slightest sound of percussion can be heard through it with ease. The lung is a very sensitive resonator for sounds within its range, a fact which is shown in its response to weak tones furnished by the larynx.

We may think of the relation of the chest wall to the lung in percussion as follows: Heterogeneous vibrations from the blow are communicated from the pleximeter to the chest wall and necessarily disturb the equilibrium of the parts struck. Rapid vibrations pass readily through the wall. But the lung is in close contact with it. Such vibrations when they reach the air cells disturb their equilibrium also, but the elasticity of the lung tissue does not permit its particles to fly back and forth in the tempo indicated. They are forced to move but they move slowly. The rapid vibrations when they meet such an obstacle are therefore in part reflected soon after penetration, producing sound waves in the localized reflections to a small extent, and thus effecting a certain reinforcement of the high pitched tones, but for the most part dying out. The chest wall vibrates to the sound waves returned from the lung, as well as to those which pass through its own tissues without

4. Jacobson and Danielopolu: München. Med. Wchnschr. **59**:216, 1912.

penetrating the lung, but acoustically speaking, it forms practically a part of the lung so that when vibrations of the two classes, the autochthonous vibrations of the chest wall and the sound waves of the lung, pass outward in all directions from the point of impact to the other portions of the wall everywhere they encounter the resistance of the underlying lung and die out. Under the conditions the walls cannot institute independent vibrations of the periodicity required for high pitched sounds because they are everywhere damped by the lung. The rapid vibrations have had little effect so far as the lung is concerned, except perhaps to furnish some energy by the disturbances which they have created. Slow vibrations, on the other hand, are not so well adapted to the normal vibratility of the wall as those which are rapid, but nevertheless are transmitted well to the lung, the structure of which permits them to pass freely, and, undergoing reflection, they produce stationary sound waves which fit from the outset the dimensions of the cavity or may be forced to adapt themselves to it. The result is a loud fundamental tone which we speak of as the reinforcement, or resonation, of the tone furnished by the resonator. What has happened, however, is in reality that the energy of a series, or several series of vibrations which in the unfavorable acoustic medium of the generator (in this case the pleximeter) could not be effectively applied is able when the vibrations reach a favorable medium to develop itself to the best advantage, so that what is perhaps a small part of the total energy of the blow creates a sound which is enormously greater than all of the other sounds of percussion.

Martini [5] criticises my [6] statement that "the sound of percussion, as it reaches the lung, contains the (its) fundamental note." This statement requires farther amplification in order to be understood. A blow on the bare chest—immediate percussion—a blow on a noiseless pleximeter of soft rubber (Selling) and blows on various other pleximeters, including the finger, laid on the chest differ as to the sounds of impact of the blow which are high pitched disharmonic partials of greater or less obtrusiveness, according to the nature of the substances that clash. But all these variations in the manner of exciting the proper vibrations of the air volume of the thorax make no difference in the pitch of the resulting tone.

A very considerable part of the energy of the blow of immediate percussion is converted into heat and friction, on account of the soft and yielding character of the skin and other soft parts of the chest wall. A stronger blow is therefore required in immediate than in mediate per-

5. Martini, P.: The Mechanism of Production of Breath Sounds, Arch. Int. Med. **32**:313 (Sept.) 1923.

6. Bushnell, G. E.: The Mode of Production of the So-Called Vesicular Murmur of Respiration, J.A.M.A. **77**:2104 (Dec. 31) 1921.

cussion to produce the same effect. The function of the pleximeter is to compress and fix, in part also to push apart, the soft parts and, usually, to furnish a more or less plane, or convex, surface to receive the blow in place of the yielding concavity of the uncovered intercostal space. When pressed firmly against the chest wall the proper vibrations of the pleximeter are so damped that they may be disregarded. Practically, the pleximeter has become a part of the chest wall, viewed as an apparatus for the transmission of sound, and the percussion note, as we hear it, is the fundamental tone of the thorax plus the sound of impact. For the same reason the hammer, or the hand, which strikes the chest wall directly is for the moment of contact a part of the same apparatus. Now, we can interpret this process, as Geigel does, and say that all that the percussion blow furnishes is energy, the lung answering to the commotion of its parts in the only way in which it can answer effectively by its proper vibrations. This is the simplest way of conveying the rôle of the lung in the production of the note of percussion and is sufficiently correct for all practical purposes. But, strictly speaking, the vibrations of the chest wall antedate those of the underlying lung. What are those vibrations? They are the only vibrations possible for the wall of a resonator, the vibrations proper to the cavity which it bounds. Therefore, speaking of the effective vibrations and admitting the existence of the vibrations peculiar to the mass of the pleximeter, we may say that the energy of the blow is converted immediately in the chest wall and in the pleximeter into the vibrations of the fundamental tone of the hemithorax. In this sense my statement is believed to be correct.

Martini's [2] experiments show clearly that disparate vibrations cannot be forced to any noteworthy extent on such a resonator as a wooden box. At the same time, Martini exaggerates the independence of the two systems, box wall and box cavity, because the tone that connects them, the fundamental tone of the cavity, is not, and from the nature of the case cannot be, clearly identified in the vibrations of the wall. There is nothing to emphasize vibrations of this frequency among the numerous other vibrations of the wall (or plate) when tested alone. When, however, the resonator is excited to action by the same vibrations the sound waves of wall and air react on one another, each strengthening the other; they become one sound which the registering apparatus cannot connect with the wall. Martini speaks of forcing vibrations on the box, whereas I believe the vibrations which are of importance in physical diagnosis are the free vibrations which call forth the fundamental tone. The vibrations forced on the lung from the bronchi are not, of course, imitated in Martini's experiments.

I have never been of the opinion, as stated by Martini, that the vibrations of the bronchial system are the excitant of the vesicular murmur, if by the phrase Martini means that the fundamental tone of the

bronchial system is forced on the thorax to the exclusion of the proper tone of the latter. It would be quite improbable that a weak and "almost musical" note of considerably higher pitch than that of the thorax resonator should act as the excitant of its fundamental tone. But, in addition to the fundamental tone of the bronchi, a number, perhaps very many, of other tones are present, for bronchial breathing is a noise. Besides their function as a resonator, the air tubes also play a part as speaking tubes down which are conducted the various kinds of laryngeal sounds. No sound waves can pass through an elastic tube without imparting vibrations to it, but these, if differing much in pitch from the fundamental tone, are of little consequence. It, therefore, would not be far removed from the truth to consider the air tubes of the bronchial system, in their relation to vibrations of the frequency of the fundamental tone of the thorax to act simply as the transmitters of such vibrations. As in percussion, so also in breathing, the sounds which are reinforced to become the vesicular murmur are not forced on the thorax but excite its free vibrations. It may be pointed out in this connection that the fact is recognized that the vesicular murmur may be distinguished in the breath sounds, as heard in tracheal breathing (von Müller [7]). It is therefore conducted through tubes, the vibrations of which have a very different frequency from that of its own vibrations, and there should be nothing in the way of the assumption that vibrations of the same frequency reach the lung by passing through the bronchi from the larynx.

I am entirely in accord with the opinion of Martini that "the bronchial breathing which is audible over solidified tissue may rightly be considered as a correctly propagated specific vibration of the air of the bronchial system." [8] Of course moisture in diseased tubes may effect changes in the sounds of bronchial breathing in the direction of roughened breathing and of musical, sonorous and other râles, but in general Martini's statement is undoubtedly correct. It is to be hoped that the adoption of Martini's standpoint will do away with the more or less absurd theories as to the effect of diseased tissue in modifying locally the character of the breath sounds that pass through it.

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7. von Müller, F.: Verhandl. d. deutsch. Kongr. f. inn. Med. **28**:184, 1911; Ztsch. f. ärztl. Fortbild. **9**:417, 1912.

8. Martini criticises with some justice my statement that "in massive consolidations of any kind the deep and medium pitched tones are suppressed." I had in mind especially the extreme cases of massive consolidation, in which, according to some authorities there is very little transmission of sound and also the statement of Müller [7] (first reference) that in pronounced bronchophony only the highest tones of the voice are audible. This author also remarks in the same paper that in pure bronchial breathing the deep tones of the large and small octaves disappear entirely. My remark was therefore not without some justification (Martini himself states in his paper in the *Deutsches Archiv* that the lower border of resonance in most cases of bronchial

Martini attacks Sahli's view that the vocal cords act like the reeds of an organ pipe to produce sounds which arouse the resonator action of the bronchi. I agree with Martini in excluding the action of the smallest bronchi and bronchioles which Sahli believes to act as resonators. But air tubes of a sufficient diameter to permit resonation cannot any more escape acting as resonators of tones of a suitable frequency than can other volumes of air enclosed within elastic walls. My experiments show that tracheal breathing disappears when the larynx is widely opened.

Martini's objection that the vocal cords are too relaxed to be able to stimulate the air current to such loud sounds as those of bronchial breathing would have weight if in order to functionate as reeds it were necessary that the cords should be tense throughout their entire mass, as in phonation. They are indeed too lax to produce musical tones but their relaxation is precisely what favors the production of noises. Their edges flutter in the air current because they are not tense, and in so doing produce the variety of incongruent tones which we call a noise. The sound is produced in a way similar to that of a wet handkerchief exposed to a gale of wind, one edge of the cloth being held tense between the hands and the opposite edge being free to vibrate. The fact that the sounds of laryngeal breathing do not rise in pitch with increase in force of the air current, so long as the position of the cords, their tension and the shape of the mouth and lips remain the same, is rightly held by Geigel[9] to prove that they undergo resonation. To this argument Martini objects, on the grounds that tracheal breathing resembles, as to its mechanism, what he calls a lip pipe rather than a reed pipe. He then goes on to set forth the properties, as a musical instrument, of a lip pipe. It appears from his exposition that the tones of such a pipe are created by blowing against a sharp edge, the pitch of the tones varying directly with the rapidity, or pressure, of the air. But, he says, these vibrations do not control the fundamental tone of the pipe which is determined chiefly by the dimensions of the cylindric cavity connected with the lip or orifice. He then goes on to say that the air current is nevertheless

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breathing lies at from 574 to 322 vibrations per second), but it was an error to make so sweeping a statement in a condensed presentation of the subject. The sentence preceding the one quoted by Martini justifies his belief that I hold that the tones of bronchial breathing are chiefly resonated in the mouth and nasopharynx. I am unable to explain my carelessness in the wording of that sentence. What I really believe, however, is shown in the preceding paragraph in which I state that "in bronchial breathing the bronchi are the resonators." Martini assumes that I think that resonance is only produced in the bronchi in disease. But I say that the bronchi function in the same way in normal breathing, and my later remark that "the conduction, not the mode of production, of these sounds is changed in disease" should make my meaning clear.

9. Geigel, R.: Leitfaden der diagnostischen Akustik, Stuttgart, Ferdinand Enke, 1908.

of influence on the tone because, with moderate pressure there arises the fundamental tone, with strong pressure the first overtone, finally even the second, etc., are produced, yet, even to cause the first overtone (the octave) much greater differences in intensity of air pressure are necessary than are ever attained in respiration. This behavior of the lip pipe, we may remark, is precisely the same in principle as that of the reed pipe which with much increased force of the air blast may be made to produce the octave of the fundamental tone and other higher overtones. The lip pipe, as Martini describes it, is substantially a resonator. And it is a resonator like the reed pipe and the human air tubes, for in all three the fundamental tone of the cavity dominates under ordinary conditions. The fact that its tones may be changed under high pressure is immaterial in this connection. What we are solely concerned with are the facts relating to weak noises produced by an air current of very moderate velocity. The chief difference between the standpoints of Martini and of myself, then, really is that Martini thinks that the representative of the lip of the lip pipe is to be found in the edges of the bronchial bifurcations within the lungs and not at the larynx. As I have shown experimentally, Martini is probably right in his supposition that edge tones may be produced in the way that he suggests, for in "reciprocating breathing" with closed glottis sounds are heard which resemble the vesicular murmur, as to pitch. But these are produced under positive pressure. This discussion will serve to emphasize the important point that the claims of the writer, as to the origin of the vesicular murmur apply solely to its production under normal conditions, as respects rate of breathing and position of the vocal cords. I have never held that the resonation of the thorax could not be aroused by other excitants than the vibrations of the vocal cords. In fact, the chief reason why my standpoint is not more readily adopted is thought to be the failure of other investigators to realize how easily sounds can be produced within the air tract, and how little specific the sound which excites the resonation of the thorax needs to be.

It must be that the thorax functionates as a resonator because it responds to excitations of various kinds with the same note, a note which varies in pitch with the size of the thorax, but is always of the same pitch in the individual thoraces, and because the cavity controls the vibrations of the walls. Another proof that the thorax is a resonator is afforded by the fact that the musical tones of phonation can only be forced on the thorax when they are of nearly the same frequency as that of its normal vibrations; they are forced the more successfully the nearer they approximate that rate. This shows that the thorax has a zone of resonance for musical tones. But the most important proof that the thorax functionates as a resonator is its relations to the sounds produced by the vocal cords. A resonator, except when struck, cannot

create sound. It is dependent on a generator for the origination of the sound and only responds to certain tones by reinforcement. It follows, of course, that if the generator is silent the resonator will also be silent. If then the vocal cords act as a generator for the thorax, acting as a resonator, suppression of their vibrations should result in the absence of thoracic sound. On appeal to experiment this is found to be the case. I was able to abolish not only laryngeal (and tracheal) sounds, but also the vesicular murmur and other breath sounds, as heard over the chest, by opening the larynx wide.

To this argument Martini opposes negative evidence, he always hears breath sounds over the trachea, as well as over the lungs, "when the respiration is rapid enough." Great increase in rapidity of breathing not only makes it more difficult to keep the larynx open, but may possibly cause sound in a new way. Beau [10] states that if the respirations are increased above forty-five per minute a sound is produced from the movement of air through the larynx, though the glottis be wide open. But of course one cannot study the vesicular murmur with such a high rate of respiration. If Martini means what might be called only a normal rapidity of respiration, it might be inquired whether this observer has practiced correctly the difficult art of keeping the larynx open? My method has not been mastered until one has learned to cause all laryngeal sound to disappear from the breathing, as controlled by self auscultation, the bell of a binaural stethoscope being applied to the side of the experimenter's larynx. When the glottis is wide open my experience shows that, the larynx being silent, the lung is also silent, provided of course that adventitious sounds of mouth or nose are also excluded. On the other hand, when the larynx continues to produce sound of any kind, that sound, as modified by the chest resonance, has been audible over the lung. Those observers who have participated in the experiment have expected, and I have exacted it of myself that all sound shall be absent from the lung, otherwise the experiment has been considered to have failed on the particular trial. It may be a question whether so thorough elimination of sound is necessary to prove the point. Laryngeal sound may persist and yet the true vesicular murmur may be absent. One of the acutest of the observers noted this fact. When I remarked, after an experiment had ended, that I had failed during a series of respirations to eliminate all sound, he replied: "a sound was to be heard, but it was plainly not the vesicular murmur." It is probably true that the elements of the laryngeal noise which are of the pitch of the fundamental note, being of the deepest tones of the noise, are best, or only, produced when the edges of the vocal cords in their full length are free to flutter. The minimal projection of a part

10. Beau, J. H. S.: Quoted by Bushnell, G. E.: The Discoverer of the Mode of Production of Breath Sounds, J. A. M. A. **80**:895 (March 31) 1923.

of the vocal cords at the time when the cords are not only under a certain tension but are also very closely appressed to the sides of the larynx might therefore very well fail to permit vibrations sufficiently low pitched to call forth the fundamental tone. However, if the above is correct it is difficult to understand why such sounds are audible through the lung.

The production of sound in tubes is easily illustrated. Remove one of the tubes of a binaural stethoscope and blow through it. With forcible blowing the sound at the free end of the tube is loud. But if one breathes through the tube a sound is produced which is louder when the air is sucked in than when it is expelled and, in fact, imitates to a singular degree the breath sounds, as heard over the chest, in that the sound of inspiration is louder and more prolonged than that of expiration.

Martini inquires: "Where else should the bronchial breathing originate after the elimination of the vocal cords through a smooth tube, such as the tracheoscope, if not in the tracheobronchial ramifications?" The answer manifestly is: "At the upper end of the tracheoscope." And the correctness of this reply would not necessarily be affected, even though it should be shown that respiration through the free tube does not produce audible sound when tested. For, when in place in the larynx it is in a resonator, more than that, in a complicated system of resonators, and slight vibrations would be powerfully reinforced. So that if Martini hears bronchial breathing over the trachea and the vesicular murmur over the chest when the tracheoscope excludes the vocal cords, the explanation is that the high pitched tones of the tube sounds are resonated in the trachea and the larger bronchi, very likely also, the highest of them, in the cavities of the mouth and nasopharynx. This gives an imitation of bronchial, or tracheal breathing. Over the chest the higher pitched tones are suppressed and only the lower tones receive resonation; this imitates the vesicular murmur. In fact, it would be correct to say that it reproduces the vesicular murmur. For there is nothing specific about the series of vibrations in a noise which are of the periodicity of the thorax. The specificity of the sound of the vesicular murmur is due to resonation within the thorax of the tone of the proper pitch, not to the sound as originally made. It is probable that noises produced in a great variety of ways contain vibrations of the proper periodicity for exciting the fundamental tone of the thorax, if introduced through an open glottis, or a tracheoscope during the respiratory movements.

Beau [11] called attention to the fact that to avoid producing sound in blowing through a tube, its internal diameter must be at least equal to

11. Beau, J. H. S.: Traité expérimental et clinique d'auscultation, appliquée a l'étude des maladies du poumon et du cœur, Paris, 1856.

that of the trachea, which is, he says, about 2 cm. And Baas many years ago published his experiments in producing sound by blowing through a tube. I can only express astonishment that later writers have ignored the obvious application of these facts to sounds which simulate breath sounds when the vocal cords are excluded.

Another source of sound due to escape of air from a small tube to a larger tube or space should be considered in this connection; sounds caused by the respiratory current of air, as it emerges from the nostrils, or passes through nearly closed lips, as well as those caused by slight relaxations of the soft palate. In practice, the auscultator is watchful to prevent such adventitious sounds. They usually mislead by exaggerating the bronchial element of respiratory sound, but there is no reason why they might not also act as excitants of the vesicular murmur, or its equivalent, when the vocal cords are excluded from action. Experiments with the tracheoscope and the like are of no value, unless the observer takes extreme pains to guard against error from this source. When the mode of formation of the vesicular murmur is studied, the subject should always be required to open the mouth widely and to avoid relaxation of the velum palati.

Martini [2] has demonstrated the fact that the percussion note of the lung, inflated to the physiologic degree, is not dependent on the size of the volume of contained air, as is true of the relaxed lung, finding that two lungs fitted snugly together in a box give no lower tone than one of them alone and that good sized portions of an inflated lung shut off from the remainder of the organ by clamping (but remaining inflated) have a note of the same pitch as that of the inflated lung as a whole.

This demonstration of the specific vibratility of lung tissue is one of the most important contributions to the knowledge of the acoustics of the lung that have ever been made. It explains certain facts in percussion of the chest, and in the auscultation of breath sounds which were formerly inexplicable. At the same time, the discovery does not affect the standing of observed facts; the new doctrine must be reconciled with what is already objectively determined. It will be necessary therefore to consider more particularly the structure of the thorax and its peculiarities as a resonator in the light of Martini's experiments.

Hitherto it has been assumed, for the sake of brevity, that the thoracic cage functionates under the same laws as resonators which are filled only with air. The fundamental law that confined volumes of air under atmospheric pressure will respond to imparted vibrations by free vibrations, the periodicity of which is determined chiefly by their volumes, undoubtedly applies to the thorax. But its structure introduces special conditions that modify this law. Resonators, as a rule, have more or less homogeneous and continuous walls which vibrate as a whole in harmony with their undivided contents. But the con-

struction of the thorax tends to prevent the communication to one of its halves of the vibrations of the other half, and to prevent also the full and free communication of localized concussions to the whole of even one half. The construction, in short, may be said to have in view chiefly the prevention, so far as possible, of the evil effects of shock.

Of thoracic structures the ribs are most exposed to the localized concussion of blows and falls. The bone of the rib is firm, but elastic enough to yield to a certain degree. The articulations with the spinal column and the costal cartilages break the continuity of vibrations. Such vibrations as are carried through these articulations, already damped in front by passing through a heterogeneous sound medium, the costal cartilages, encounter the sternum, a combination of bone and cartilage, which tends to disperse them and, lower down, the connections of the costal arch in part damp the vibrations, in part distribute them to adjoining ribs. The hoops of this part of the thoracic barrel are incomplete, not surrounding the entire circumference. Posteriorly, the structure of the spine with its disks of cartilage prevents free dissemination of vibrations up and down the spinal column; the articulation of each rib with two vertebrae halves the effect of vibrations traveling along individual ribs, with a halving also of vibrations which have passed through a vertebra to the ribs of the other side. Vibrations are also damped by the structures of the mediastinum, for the most part elastic and movable tubes and cavities, and by solid, yet movable organs which constitute the base of the thorax. The two lungs are, moreover, nowhere in actual contact with each other. The general principle of construction is to erect nowhere absolute barriers and to permit vibrations to pass everywhere, but, at the same time, to minimize their violence by reflecting them in many ways and at many places. We may say, therefore, that vibrations of the hemithorax are not communicated readily to the other hemithorax and that it is not to be expected that the two hemithoraces will vibrate freely in unison from concussion imparted to one of them. The results of percussion are such as are to be expected from the anatomic structure. If the undivided thorax vibrated as a resonator, the sound of percussion would be heard equally well over both of its halves, but we do not dream of listening to its note on the other side, and even on the same side the vibrations are often not generalized so far as our perceptions are concerned. Practically, in percussion it is the hemithorax, not the thorax as a whole, that functionates as a resonator.

What is true of the whole thorax is true also of its halves, viewed as independent acoustic units. The anatomic structure of the hemithorax is adapted, not to facilitate vibration of its several portions as a whole to communicated concussions, but on the contrary to prevent to a

considerable degree shocks imparted to one portion from being communicated to other portions.

The sound of percussion over the anterior surface of the hemithorax is not heard loudest over the back on the same horizontal level, that is, after passing through the thorax on the shortest line, but higher up and in the same intercostal space. According to Martini,[12] bronchial breathing is propagated farthest from its place of greatest intensity along a rib that cuts this place, less upward and downward in other intercostal spaces. These observations show that, while the sound of the lightest percussion is to be heard over the entire chest posteriorly, a very considerable part of the vibrations pass to the nearest ribs and by them are conveyed upward and backward in their course around the lung. The vibrations of concussion of the anterior thorax are therefore largely conducted away from the base of the upper lobe and do not reach the lower lobe in their full force at all. Posteriorly, a concussion is carried downward as well as forward through the predominating influence of the ribs and reaches the anterior lobe, if at all, near its base where the energy of the vibrations is dissipated along the costal border and such vibrations as penetrate the lung are damped by solid organs.

The disposition of the lung lobes tends to the same end. They are separate from one another, except at the roots of the lung and are surrounded by a lubricated membrane, the arrangement, like a joint, checking the free passage of vibrations. The upper lobe is alone implicated by a blow in front, the lower lobe, except near the summit of the lung, is alone implicated by blows from the rear. It may be said, in general, that the arrangement of the pulmonary lobes is calculated to shield, as far as may be, one lobe from full participation in concussions imparted to another lobe.

The percussion stroke, then, tends to be localized in its effects, the blow must be heavy to bring out the full thoracic resonance, yet the tone elicited by a light blow is the fundamental tone of the thorax. Martini's doctrine of the specificity of the vibrations of lung tissue must be accepted, not only because it is the result of careful experimentation, but also because it alone can reconcile observed facts.

In discussing this theory farther, it will be necessary to consider the properties of the lung as a vibratile organ. In complete pneumothorax the cavity has a tympanitic note if the air is not under positive pressure; with moderate pressure the note is dull tympanitic; with higher pressure the note is dull. The pneumothorax cavity, therefore, obeys the general law; it responds to percussion with its fundamental

12. Martini, P.: Studien über Perkussion u. Auskultation, III. Auskultation, Deutsch. Arch. f. klin. Med. **139**:257, 1922.

tone until increased tension prevents the vibration of its walls, the tone being of the same, or nearly the same, pitch, so long as it is audible at all. But the note of the normally expanded lung is nontympanitic; the predominating tone is still that fundamental for the air volume, but of the air volume as modified by the peculiar lung structure. The fact that the air space is multilocular does not account for this. For, if a cavity be lightly stuffed with horsehair, shavings, or feathers, so as to divide the air space into numerous small air spaces the note of percussion is still that of the whole air volume. The anatomic structure of the lung does not prevent its air space from vibrating as a whole, because the relaxed lung has a tympanitic resonance, and pieces of lung yield the same resonance which is the higher in pitch the smaller the piece.

If, however, the exenterated lung is blown up to the physiologic degree of tension, the note of percussion is no longer tympanitic, but has the same quality of sound as the normally distended lung. One might draw a parallel between the lung and the pneumothorax cavity, and say that in both cases the loss of tympanitic resonance is due to increase in tension which impairs the vibration of the walls of the resonator. But there is this difference that in the one case the tension of the air, and in the other of the solids, of the cavity is increased. The air of the pneumothorax is under positive tension and, the walls of the resonator being relatively firm and unyielding to distension, the note quickly changes in the direction of dulness as the pressure rises. Whereas, in the normally distended lung, from the nature of the case, during respiration the air pressure cannot rise above that of the atmosphere. When the exenterated lung is inflated so that the air cells are distended, and the tension of their walls approaches the normal tension, the sonority of the note of percussion is increased, rather than diminished, for, a membrane requires to be stretched in order that, as a wall of a resonator, it may vibrate to the best advantage, as is seen in the case of the drum head. If, however, the air pressure is sufficiently increased, the inflated lung becomes dull in the same way as the pneumothorax which is under high positive pressure (Martini).

It may be remarked here that the initial expansion of the lung at birth is effected largely by positive pressure. The accoucheur wishes the child to cry in order that the lung may be well dilated. That is, by straining against a closed glottis or through tense and slightly open vocal cords, the child creates a positive pressure which forces the lung into intimate contact with the walls of the thorax, where it is held thereafter during life by the pressure of the atmosphere.

According to Martini, the acoustic properties of lung tissue are responsible for the pitch of the percussion note. There can be no question, however, that the pitch of that note is not determined by the specific properties of lung tissue as such, but that it is controlled by the

size of the air volume of the thorax just as inevitably as in the tympanitic resonance of the pneumothorax cavity. For the pitch of the lung note varies with the size of the lung. It is deep in men, high in women and higher in children. We must suppose therefore that the pitch of the lung and of the larger subdivisions of lung tissue changes constantly during the growth of the child from infancy to manhood or womanhood, under the governing influences of the vibrations of the air volume of the chest. The problem, then, is to determine how it comes to pass that the vibrations of the lung tissue adapt themselves to the dominating vibrations of the air volume of the thoracic cavity.

We have seen that the anatomic structure of the thoracic cage and the manner in which the lung is subdivided into lobes are such as in part to reflect and in part to disperse the vibrations of shocks in order that the hemithoraces may not suffer from the too great violence of vibrations proper to their respective air volumes. It is manifestly necessary that the finer structure of the lung should have a similar protection, that it also should be shielded against too violent proper vibrations of the resonator in which it is situated. And it is also equally desirable that the specific vibrations of its structure shall coincide in periodicity with that of the air volume of the hemithorax. For, if each subdivision of the lung had the fundamental tone of its contained volume of air there would be a different rate of vibration for each subdivision, and there would consequently be strains at the points of juncture of the vibrating bodies. It would be intolerable if a sharp blow, for example, excited vibrations in the part of the lung directly involved which were foreign to the vibrations of adjacent parts of the lung and of the hemithorax as a whole.

The air cells of the lung must necessarily be delicate structures in order to perform their function of aeration. A homogeneous mass of air cells filling the cavity of the hemithorax would vibrate as a whole to imparted concussions, the lung would quiver like a jelly under the slightest shock from the chest wall. But the bronchial tree introduces a heterotropic element. The air tubes are strong and elastic structures filled with air, which from its smaller volume does not vibrate with and therefore to some extent damps the general thoracic vibrations. The bronchi by their disposition and their structure thus tend to reflect a portion of the vibrations which pass through the thorax. The connective tissue envelopes of lobes and lobules primarily form frameworks to strengthen the lung, but also check and tend to reflect vibrations which pass through them. It may be said, then, that the lung from its structure is an organ which is so constituted that, while it is capable of vibrations as a whole, it nevertheless damps and reflects throughout its mass a portion of those vibrations in the same manner, *mutatis mutandis*, as the chest wall. Lung tissue, containing many heterotropic bodies,

vibrates with some difficulty, that is, at a slow rate. This tends to assimilate its periodicity to that of the thoracic cavity, but does not account for the intimate relationship of the two series of vibrations.

Supposing that the bronchi and the fibrous envelopes of the lung were so thick that they reflected nearly all of the vibrations locally at various points throughout its mass. The result would be the division of the lung tissue into subordinate acoustic subdivisions, each of which would vibrate at the rate peculiar to its air volume. These subdivisions would naturally vary in size, and would therefore have different rates of vibration the result of which would be a conflict of vibrations at the juncture of the individual subdivisions, none of which, moreover, would vibrate at the rate peculiar to the lung mass as a whole. Shocks and other vibrations would then produce an irritation at the boundaries of subdivisions and the high rate of vibration of the localized acoustic spaces would be injurious to the contained air cells. The part directly exposed would also bear more than its share of the concussion. Once built too strong there would be no remedy, for irritation could only be countered by proliferation which would make the partitions stronger and thicker than before. Nature's only way, therefore, is to begin with delicate structures and thicken them as the indications arise. The lung of the new-born infant is, we may suppose, adapted at the beginning of its function to its work, from its structure it reflects locally, as well as permits the passage of vibrations, to the proper degree, as determined by the size of the individual thoracic cavity. The facts show that there must be an adaptation of its specific vibratility to the volume of the lung as the latter increases in size during growth.

In full normal respiration the hemithoraces vibrate in resonation as undivided wholes; the sounds of respiration are heard over all portions of the lungs. But in quiet breathing with the upper lobes the breath sounds are faint or inaudible over the lower lobes and, conversely, when the breathing is almost purely diaphragmatic it is difficult to hear it over the upper part of the chest. This must be due to the fact that the vesicular murmur is loudest where the tension of the lung is best for its production. In other words, in such breathing the vibrations of the lung are strongest in its more expanded portions. But the vibrations, though they may not be audible as sound waves, are nevertheless communicated to all portions of the lung. We may fix a line beyond which they are not heard, but in fact there is no line of demarcation because all portions of the resonator vibrate to its fundamental tone and this is of course also true when this tone is called forth by percussion. But this is only true for the reason that the specific vibrations of lung tissue are of the same periodicity as the fundamental tone of the lung. As we saw with regard to percussion, it would be a source of irritation if localized breathing produced localized (and therefore higher pitched)

tones. For the best conditions the vibrations of the fundamental tone must shade off through the lung, meeting no foreign vibrations with which to conflict. The problem is the same as in percussion, to make the vibrations of the part equal to those of the whole. The defense against external shock is, of course, operative here, in that the lung tissue vibrates more slowly in proportion to the thickening of tubes and partitions. But in breathing, the vibrations from the larynx are introduced behind all partitions and through all tubes. Strength of partitions and weight of tubes may suffice for the best adaptation to resist external violence, but may not be sufficient for the prevention of a too generalized vibration of lung cells nor for the harmonizing of localized vibrations of parts with the generalized vibrations of the whole lung. If further and more exquisite adaptation is requisite we may think of the tuning as effected on the principle of the weighted string. A string that is weighted vibrates more slowly than an unencumbered string of the same length and size, that is, has a lower tone. In the piano, for example, in order that strings for the deepest tones may not have an inordinate length, the wires are wrapped with smaller wire. As the thorax grows larger, the bronchial tubes and the fibrous partitions increase in thickness in proportion to the increase in size. If in this growth they remain too light, jarring vibrations are a stimulus to greater proliferation. The slight but unending vibrations of the breath sounds are, it may be conjectured, one of the most important of such stimuli. Probably there is no lagging in development, nor ever any marked discrepancy in vibratility between different parts of the lungs as they develop. Rather, the increased weighting of lung tissues, as required for unison of vibrations, takes place *pari passu* with the growth, the vibrations of the breath sounds being perhaps the most potent stimulus to a proliferation which in developing the growing tissues shall add just the correct amount of weighting to keep the tissues at the proper pitch, so that all portions of the lung shall always be attuned to the dominating, because most incessant, vibrations to which they are exposed.

Lest it be thought that the expression "tuning" of the lung implies an accuracy like that of the skilled violinist—an accuracy which would seem impossible of attainment under the conditions—it should be remarked that, in view of the difficulty in determining the exact pitch of low tones it is quite possible that the percussion note of acoustic subdivisions of the exenterated lung only approximates the pitch of the fundamental tone. While the fundamental tone of percussion and of vesicular breathing is easily to be distinguished as a tone, the sounds of percussion and of respiration still remain noises which shows that, besides the fundamental tone, various other tones of low pitch are forced on the resonator, its response therefore being with a zone of resonance, not with a single tone. The lack of a clear musical tone and the irregu-

larity of curve of the normal thoracic note both in percussion and in respiration, as contrasted with tympanitic resonance, might perhaps be best explained by the persistence of tones which arise from individual acoustic subdivisions. We would think of the process in this way: Each subdivision varying in size from the other subdivisions, in their reflection of a portion of the vibrations which reach them, produce tones of slightly different pitch. But sufficient vibrations pass through the reflecting surfaces to excite the normal response of the thorax by its fundamental tone which, being reinforced to the best advantage, is able to force itself on such of the subdivisions as have a slightly different fundamental tone, but not to the extinction of the latter tones. It is also to be remembered that the optimal expansion of the lung tissue plays a part, as experience shows, in at least the loudness of the vesicular murmur. It is therefore to be expected that, as the lung tension varies during an inspiration in the part of the lung over which the registering apparatus is placed, the strength of the tones resonated by the individual subdivisions will have varying degrees of prominence in the complex.

The lung tissue is protected against the vibrations of voice sounds of higher pitch than that of its fundamental tone by the fact that these are resonated in the bronchi, only the deep notes of a bass voice including the fundamental tone of the thorax. The slowness of these low pitched vibrations prevents injury from too rapid oscillations of lung tissue, but nevertheless the strong vibrations of the lowest pitched organ tones are disagreeable to men whose thoraces respond to such deep tones. What the effect would be if the higher pitched tones of the voice received resonation in the air cells may be inferred from the very unpleasant sensation from "ear piercing" tones, those of or near the fundamental tone of the tympanic cavity, although in the ear the function of the tympanum as a resonator is minimized by its smallness, the irregularity of the cavity and the soft mucous membrane that covers its walls. The intermittency and the wide range of tones of the voice would probably prevent such tones as may be forced on lung tissue from exercising much effect on the lung structure in its acoustic relations.

The fact that, when the glottis is opened wide the chest is silent in respiration, of course overthrows existing theories as to the mode of production of the vesicular murmur by vibrations originating in the lung tissues. Two theories will, however, be referred to briefly, those of Geigel [9] and of Martini,[12] respectively.

According to Geigel's theory, the vesicular murmur is the sum of the noises of innumerable miniature explosions due to the dilatation of air cells in inspiration and also to the sound of their mutual jostlings as they interfere with one another in their expansion. This theory, as enunciated by Geigel, provides only for the sound of inspiration. To complete the explanation Sahli suggests that the air cells jostle each other also during expiration as they return to their position of rest.

The obvious objections to this theory are: first, that the air cells do not collapse in expiration but remain partially filled with air, there can therefore be no tearing apart of adherent surfaces, nothing that resembles an explosion, in inspiration. Second, that the structure of the lung parenchyma gives no support to the idea that air cells jostle one another either in inspiration or in expiration, as if they were a parcel of dried bladders.

According to Martini,[12] the specific vibrations of lung tissue do not appear as the responses of a resonator to the sounding of its fundamental tone but are "of great importance in originating the inspiratory breath sound which is audible over the air bearing lung." He compares the percussion sound with the string of a musical instrument which has been struck, and the vesicular murmur to the sound produced by a string of the same length, the tension of which has been suddenly increased, both methods of exciting the vibrations of the string giving the same tone. Elsewhere he accounts for the persistence of the vesicular murmur in expiration by the fact that a string produces a slight sound when suddenly relaxed. To strengthen this comparison he speaks in both passages referred to of the suddenly expanded or distended lung. But the lung does not as a rule expand suddenly in inspiration. No theory is acceptable which does not account for the presence of the vesicular murmur in slow and easy respiration. The comparison with the struck and tightened strings has the weight only of an analogy. The analogy consists in fact that a stretched string, so long as its length and tension remain unchanged, will always emit a tone of the same pitch whatever excitation may call forth that tone. Each string, in other words, has a fundamental tone depending on its length, just as in general the tone of an organ pipe depends on its length. Martini nowhere gives any indication of the precise mechanism by which the lung would be enabled to produce the sound of the vesicular murmur, further than to state that the lung is brought out of its equilibrium in respiration, and in endeavoring to recover this state of equilibrium vibrates about it periodically and with the same fundamental frequency which is simply the explanation usually given of the production of sound by an elastic body. He furnishes no clue as to the way in which the equilibrium of the lung is disturbed, so as to produce sound in respiration, further than to say that the proper vibrations of the lungs are brought about by the enlargement of the chest in inspiration and its decrease in expiration.

SUMMARY

1. A volume of air confined within elastic walls responds to excitations by a sound, the most important element of which is the tone proper to the dimensions of the cavity. Such cavities may be called resonators in the widest sense of that word.

2. The human thorax is such a resonator. But it differs from other resonators in that it contains solid structures which, when the lung is physiologically active, are under a definite tension.

3. The theories as to the mode of production of the normal vesicular murmur have been unsatisfactory. The proof that the thorax functionates as a resonator is afforded by experiment.

4. Sound may be forced on a resonator in two ways: (1) A somewhat different rate of vibration of the generator may change the fundamental tone of the resonator, it is out of tune; (2) Without alteration of its fundamental tone the resonator may also respond simultaneously to other series of vibrations, its response is a "noise." That the normal sounds of respiration are noises is probably in part due to this cause.

5. Resonators may be excited to the production of the fundamental tone in three ways: (1) The resonator may be struck. An example is the percussion note; (2) A tone of the frequency of the fundamental tone of the resonator may be presented to it for reinforcement. An example is the vesicular murmur; (3) Musical tones of different pitch may be forced on the resonator within a limited range and produce a change in pitch of the fundamental tone. An example is vocal resonance; (4) If the resonator responds strongly to vibrations of, or near, the rate of its normal vibrations, there may be a sympathetic vibration of its walls apparent to the touch. An example is vocal fremitus.

6. The theory of the dependence of the thorax, as a resonator, on sounds produced in the larynx applies only to the relatively weak and slow air currents of *normal* breathing. The phenomena of "reciprocating breathing" show that sound may originate in bronchial tubes through which air is strongly forced.

7. The specific characters of the vesicular murmur are due, not to the generator of the sound, but to the resonator. Any sound produced within the air passages during normal respiratory movements of the thorax may excite what amounts to the vesicular murmur, though the vocal cords are excluded from action by a laryngeal tube.

8. The structure of the thoracic walls and of the lungs is such as to tend both to localize and to disperse the vibrations of imparted shocks.

9. It is necessary that the lung shall be so constructed that the rate of vibration of its parts shall be equal to the rate of vibration of the whole lung, and that the rate of vibration of the latter shall be the same as that of the cavity within which it lies.

10. This requires a constant readaptation of the lung, as it develops within a growing thorax, to the fundamental tone of the cavity.

11. The experiments of Martini have demonstrated a specific rate of vibration of physiologically inflated portions of the lung, which is the

same as that of the whole lung inflated in the same way and does not differ whether the lung be tested within or without the cavity of the hemithorax.

12. Another peculiarity of the human thorax considered as a resonator consists in the fact that it contains a system of smaller resonators, the air tubes, which are more or less perfectly insulated by envelopment with lung parenchyma. This insulation which is thicker in some parts of the lung than it is in others may be impaired or destroyed by disease.

13. The phenomena observed in the physical diagnosis of the diseased lung depend largely on the impairment or destruction of the insulating parenchyma with impairment or loss of its specific vibratility and, consequently, with improved transmission of bronchial sounds.

14. In general, the transmission, not the character of breath sounds is altered in disease.

Book Reviews

A CLINICAL GUIDE TO BEDSIDE EXAMINATION. By Dr. H. Elias, Dozent and Assistant at the First Medical Clinic of the University of Vienna; Dr. N. Jagic, Extraordinary Professor and Chief Physician to the Sofienspital, Vienna; Dr. A. Luger, Dozent and Assistant at the Second Medical Clinic of the University of Vienna. Translated by William A. Brams, M.D., Adjunct in Medicine, Michael Reese Hospital, Chicago, Illinois. Cloth. Price, $1.50. New York: Rebman Company, 1923.

As the title suggests, this book is intended as a guide to bedside examination only, no detailed descriptions, theories or procedures requiring laboratory, graphic or other instrumental aid being discussed. In short, only such information as can be obtained by the methods of inspection, palpation, percussion and auscultation is given. A general schema of a physical examination at the bedside serves as an introduction. This is followed by a detailed consideration of each and every portion of the outline. It is very comprehensive, and there are no misstatements of fact. The authors apparently have made a strong plea for more careful general physical examinations, relying as far as possible on these methods for a diagnosis with the idea of supplementing the information obtained with such adjuncts as the various laboratory tests, graphic records and instruments of precision. Greater uniformity and completeness will obtain in the examination itself and the history records by adopting such a schema.

THE DIETARY OF HEALTH AND DISEASE. By Gertrude I. Thomas, Instructor in Dietetics, University of Minnesota. Cloth. Price, $2.25. Pp. 210, with illustrations and tables. Philadelphia and New York: Lea and Febiger, 1923.

The purpose of this book is to provide an intermediate text as a basis for instruction in schools of nursing or departments of home economics, and is intended for the use of dietitians, nurses and instructors in the sciences that pertain to nutrition. A short outline of a course in dietetics is given, and the outline form is used throughout the book. The physiology of food in its relation to the human body, the several phases of food chemistry, food preparation and dietotherapy are presented in a very comprehendable yet concise manner. The chapters on special diets are exceptionally well written. An excellent bibliography is appended to each chapter.

CORRECTION

In the article of Drs. A. W. Meyer and F. A. Cajori, in the May issue, page 581, "F. A. Cajori, M.D.," should read "F. A. Cajori, Ph.D."

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